

MICROVASCULAR PATTERNS
AND BLOOD SUPPLY
OF HEPATIC TUMOURS

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Lund 1984



Organization LUND UNIVERSITY Department of Diagnostic Radiology University Hospital, S-221 85 Lund Sweden	Document name DOCTORAL DISSERTATION Date of issue September 7th, 1984 CODEN LUMEDW/(MEXL-1013)/01-69/(1984)
Author(s) Gui LIN	Sponsoring organization
Title and subtitle Microvascular patterns and blood supply of hepatic tumours.	
Abstract The vascular supply of liver tumours was investigated by 3 methods. A) Sixteen human cadavers with liver metastases were examined by perfusing Microfil into the hepatic artery and portal vein. A total of 107 metastases between 1 and 20 mm in diameter were investigated. In addition, 23 metastases examined with Microfil were compared with the histological sections. B) Selective angiography was performed in 94 patients with a clinical diagnosis of hepatic carcinoma. C) Selective angiography, embolization, and Microfil preparation were performed in 20 rats with implanted liver tumours. The following observations were made: 1) Most metastases had both arterial and portal blood supply, although the arterial supply prevailed. The same type of metastases could be filled either from the hepatic artery or portal vein. 2) The vascular patterns of the metastases varied in different livers, but nodes from the same liver had the same type of tumour vessels. The number of tumour vessels decreased in the centre with increasing size of the tumour. The Microfil preparations corresponded well with the histopathological sections. 3) Filling of tumour lakes from the portal vein was observed more often in embolized rat livers than in their controls. 4) Some of the findings at angiography and CT could be explained by the present investigation. In view of a dual supply of hepatic tumours, there is reason to believe that treatment of these tumours should be given via both the hepatic artery and the portal vein.	
Key words Hepatic artery - Portal vein - Liver tumours - Embolization - Microfil preparation - Histopathology - Angiography - CT	
Classification system and/or index terms (if any)	
Supplementary bibliographical information	Language English
ISSN and key title	ISBN
Recipient's notes	Number of pages 69
	Price Security classification

Distribution by (name and address) Dr Gui LIN, Department of Diagnostic Radiology, University Hospital, S-221 85 Lund, Sweden

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G U I L I N
M.D., Lund

Akademisk avhandling som med vederbörligt tillstånd av
Medicinska Fakulteten vid Universitetet i Lund
för avläggande av medicine doktorsexamen kommer att
offentligen försvaras i Föreläsningssal 3, Centralblocket,
Lasarettet i Lund, fredagen den 7 september 1984, kl 13 15.

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MICROVASCULAR PATTERNS AND BLOOD SUPPLY
OF HEPATIC TUMORS

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Lund 1984

The British language in the Summary was revised by
Dr Curt G Carlbon

This thesis is based on the following papers:

- I. GUI LIN, ANDERS LUNDERQUIST, INGA HÄGERSTRAND and ERIK BOIJSEN: Post-mortem examination of the blood supply and vascular pattern of small liver metastases in man.
Accepted for publication in Surgery
- II. GUI LIN, INGA HÄGERSTRAND and ANDERS LUNDERQUIST: Portal blood supply of liver metastases.
Accepted for publication in American Journal of Roentgenology
- III. LEIF EKELUND, GUI LIN and BENGT JEPPSSON: The blood supply of experimental liver tumors following intraarterial embolization with gelfoam powder and absolute ethanol.
Accepted for publication in Cardiovascular and Interventional Radiology
- IV. GUI LIN, ERIK BOIJSEN, INGA HÄGERSTRAND and ANDERS LUNDERQUIST: Microvasculature architecture of small liver metastases in man. A correlation between Microfil vascular preparations and histologic sections.
Investigative Radiology
- V. GUI LIN, TORBJÖRN GUSTAFSON, INGA HÄGERSTRAND and ANDERS LUNDERQUIST: Low density ring in liver metastases on CT.
Accepted for publication in Journal of Computer Assisted Tomography
- VI. LIN GUI, HAN XIN-YE, GU JIN, RONG DU-SHAN, WANG SHOU-ZHONG, WANG GONG-XIAN and CHEN XING-RONG: Selective angiography in diagnosing primary hepatic carcinoma.
Chinese Medical Journal 95 (1982), 667 - 673

Reference to these papers will be made by the numerals I - VI.

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Introduction

The results and information obtained from the literature regarding the blood supply of hepatic tumours have been controversial /1, 2, 4, 7, 17, 21, 22, 30, 33/. BREEDIS and YOUNG /7/ studied the blood supply of liver tumours in animal experiments and in man by means of dye injection. They concluded that the hepatic neoplasms are supplied exclusively by the hepatic artery. Evaluating blood dynamics and time-density curves of hepatocellular carcinoma, HOSOKI et coll /20/ came to the same conclusion. Also other investigators /10, 34/ maintained that all human hepatic tumours receive their blood supply exclusively from the hepatic artery.

ACKERMAN et coll /1, 4/ studied microvascular patterns and blood supply of experimental hepatic tumours in rats by perfusing Microfil into the hepatic artery and the portal vein. They found that hepatic tumours, particularly small liver tumours, have a dual blood supply.

HONJO and MATSUMARA /18/ pointed out, after studying induced primary hepatic tumours by infusion of dye solution into the hepatic artery and portal vein, that a typical cholangioma was nourished by arterial blood, whereas a hepatoma received a dual blood supply.

NILSSON and ZETTERGREN /28, 30/ investigated the blood supply of induced primary hepatic carcinoma and the effect of hepatic artery ligation in rats. They demonstrated that ligation of the hepatic artery often resulted in total necrosis of cholangiocellular carcinoma.

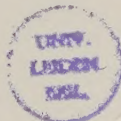
The aims of the present investigation were:

1. To show microvascular patterns of small liver metastases and their blood supply in man /I=27/.
2. To investigate how liver metastases receive their blood supply from the portal vein /II=25/.
3. To disclose the portal blood supply of experimental hepatic tumours after intra-arterial embolization /III=13/.
4. To explain some findings of hepatic tumours on angiography and contrast-enhanced computed tomography /IV=23; V=24; VI=26/.

Material and methods

The present investigation consists of 3 parts: liver perfusion with Microfil in human cadavers /23 - 25, 27/; experimental study in rats /13/; and selective arteriography in patients with primary hepatic carcinoma /26/.

Liver perfusion with Microfil in man /23 - 25, 27/. Sixteen human livers with metastases of various sizes and origins were examined at autopsy. The primary sites included carcinoma of the breast (5 cases), lung (3 cases), colon (2 cases), prostate (2 cases), pancreas (1 case), gall bladder (1 case), and malignant lymphoma (2 cases). There were 10 males and 6 females, age ranging 35 - 86 years.



Immediately after the entire liver had been removed from the fresh cadaver, the portal vein and the hepatic artery were exposed and cannulated with a polyethylene catheter. There was no preliminary washout of the vessels. Microfil (Canton Bio-Medical Products, Boulder, Colorado, USA) was injected manually until the vessels appeared to be well filled. When Microfil flowed out from the hepatic veins and small vascular structures could be well demonstrated on the surface of the liver, the infusion was stopped. The volume of Microfil used depended on the size of the liver. As a rule, 30 - 40 ml and 40 - 50 ml were enough to perfuse the hepatic artery and the portal vein, respectively.

White or yellow Microfil (MV-112 or MV-122) was usually first injected into the portal vein, then orange Microfil (MV-117) into the hepatic artery of the same lobe (Table 1). If the hepatic artery and the portal vein were perfused subsequently in the same lobe (11 livers), additional curing agent was added to the first injected material to accelerate the curing process. The second injection was performed 2 - 3 hours later to prevent mixing of the 2 colours.

In 2 livers, injection was made only into the hepatic artery and the portal vein, respectively (cases 3 and 4).

After the injections were completed, the specimens were kept in a refrigerator overnight. The liver was then cut and pieces containing metastatic nodules surrounded by normal parenchyma were dehydrated in increasing concentrations of ethanol, 1 - 2 days in each of 25 %, 50 %, 75 %, 95 %, and 99.5 % ethanol. Finally, the specimens were placed in methyl salicylate for clearing. When the specimens became transparent, they were examined under a stereomicroscope.

A total of 107 metastases measuring less than 2 cm in diameter were obtained for special examination. Among them, 101 metastases were less than 1 cm in diameter.

Twenty-three specimens (in 12 livers) were then treated with decreasing concentrations of ethanol, embedded in paraffin, sectioned, and stained with haematoxyline-erythrosin, and sometimes with reticulin and/or collagen stains for histopathological examination.

Experimental tumour study in rats /13/. Twenty Wistar rats weighing 200 - 250 g were used for the investigation. Under ether anaesthesia, 0.1 ml of a standard cell suspension containing 1.0×10^6 cells in N-Methyl-N-Nitroso-guanidine was injected into the central lobe of the liver through a midline incision inducing transplantable adenocarcinoma /15/.

Twenty liver tumours ranging in size between 0.7 and 2.5 cm were examined. The rats were divided into 3 groups. The first group (control group) included 8 rats, the second group (gelfoam group) 4 rats, and the third group (ethanol embolization group) 8 rats.

Selective angiography and embolization. On the ninth to nineteenth day after tumour inoculation, the rats were examined with selective coeliac or hepatic angiography according to a technique described previously /16, 17/. For the coeliac artery 0.3 to 0.5 ml of Isopaque Cerebral (Nyegaard A/S, Oslo, Norway) was injected manually and 0.2 - 0.3 ml for the hepatic artery.

Following baseline angiography, the coeliac or hepatic artery was embolized with gelfoam powder (Spongostan, Ferrosan Int., Copenhagen, Denmark) or absolute ethanol in a group of 12 rats. For gelfoam embolization 0.1 - 0.15 ml of gelfoam powder (1 mg gelfoam powder in 4 ml of contrast medium) was injected under fluoroscopic control /18/. For ethanol embolization 0.2 - 1.0 ml of 95 % ethanol was injected slowly manually. To confirm occlusion of the hepatic artery, coeliac angiography was repeated 15 minutes after embolization in 3 rats (gelfoam group) and in 7 rats (ethanol group). Postembolization angiography failed in another 2 rats (one each in the ethanol and the gelfoam group) owing to dislodgement of the catheter.

Microfil injection. Post-mortem Microfil perfusion was performed in all 20 rats. Our technique for Microfil perfusion was similar to that of ACKERMAN /3/. The aorta and portal vein were exposed and cannulated with a catheter (OPP 10, OD/ID 0.65/0.25 mm) and the vessels were perfused with Microfil. Orange Microfil was injected into the hepatic artery and yellow Microfil into the portal vein. The principle and technique for the tissue-clearing procedure were similar to that previously reported in the cadaver liver /27/.

Selective arteriography in patients with primary hepatic carcinoma /26/. Selective arteriography was successfully performed in 94 patients with a preliminary or definite clinical diagnosis of hepatic carcinoma. Of the 94 patients, 87 were males and 7 females with an age range of 18 - 67 years.

According to Seldinger's technique, coeliac angiography was done in 79 patients and common hepatic angiography in 7. In 4 patients common hepatic angiography was performed following coeliac angiography, and in another 4 superior mesenteric angiography was done following the coeliac injection.

Urografin® (Schering) 76 % was used, 40 - 60 ml for coeliac or superior mesenteric angiography and 30 - 40 ml for common hepatic angiography. A Gidlund high-pressure injector was used, giving an injection rate of about 12 ml/s for coeliac or superior mesenteric angiography and 5 ml/s for common hepatic angiography. Serial films were taken at a rate of one film per second for 5 seconds followed by one film every other second for 20 seconds.

The relationships between AFP (alphafetoprotein), isotope scans, and arteriograms of 88 patients were analysed.

Results

Liver perfusion in man. Tumour perfusion with Microfil (Tables 1, 2). Tumour perfusion exclusively from the hepatic artery was observed in 13 tumour nodules examined in 12 cases (out of a total of 86 tumours) in which both the portal vein and the hepatic artery were injected. Only hepatic artery perfusion was seen in 4 tumour nodules (cases 5 and 6) of a total of 62 examined in which the portal vein was first injected followed by the hepatic artery injection (cases 5 - 13), whereas it was seen in 6 out of 12 nodules in which the hepatic artery was the first vessel to be injected followed by the portal vein injection in the same lobe (cases 14 and 15).

Table 1. Liver perfusion with Microfil in 16 cases.

PV = portal vein, HA = hepatic artery.

Case No.	Primary site	Injection		Tumour perfusion			Total
		First	Second	HA	PV	Both	
1	Breast Right lobe Left lobe	PV	HA	6	4		10
2	Myeloma Right lobe Left lobe	PV	HA	1	2		3
3	Colon	HA		2			2
4	Prostate	PV			6		6
5	Gall bladder	PV	HA	2		3	5
6	Lung	PV	HA	2		1	3
7	Lung	PV	HA			24	24
8	Lung	PV	HA			3	3
9	Pancreas	PV	HA			5	5
10	Colon	PV	HA			7	7
11	Breast	PV	HA			2	2
12	Breast	PV	HA			12	12
13	Lymphoma	PV	HA			1	1
14	Breast	HA	PV	5		5	10
15	Breast	HA	PV	1		1	2
16	Prostate	HA simultaneously	PV	3		9	12
				22	12	73	107

Table 2. Distribution of tumour perfusion observed in 16 cases (107 nodules). HA = hepatic artery, PV = portal vein.

Injection	Nodules	Tumour perfusion from		
		HA	PV	Both
Via HA	9	9		
Via PV	12		12	
Via both	86	13		73
First PV, second HA	62	4		58
First HA, second PV	12	6		6
Simultaneously HA, PV	12	3		9

Table 3. Liver perfusion with Microfil in 20 rats.
HA = hepatic artery, PV = portal vein.

Group	No. of animals	First injection via PV	Vascular lakes filled by PV (%)	
Control	8	5	1	20 %
Gelfoam	4	4	2	50 %
Ethanol	8	7	6	85 %

Tumour perfusion exclusively from the portal vein was not observed in any of the cases in which both the portal vein and the hepatic artery were injected. In 3 cases in which only the portal vein was injected, all 12 tumours examined showed extensive filling of tumour vessels.

Perfusion of tumour vessels from both the hepatic artery and the portal vein was observed in 73 of 86 tumours examined. Vessels in the periphery of the tumours were usually filled with Microfil of arterial and portal venous origin, the centre usually only from the arterial side.

In 2 cases in which the portal vein of one lobe and the hepatic artery of the other lobe were injected separately, extensive filling of tumour vessels was observed in both lobes - in one lobe from the hepatic artery, in the other from the portal vein.

Microvascular patterns of tumours. In small liver metastases, the vascular pattern of the tumour nodules varied in different livers, but nodules from the same liver had the same type of vessels /27/.

The correlation between Microfil vascular preparations and histological sections was studied in 23 specimens of 12 livers /23/. Among the 23 specimens, 8 were hypervascular, 5 moderately vascular, and 10 were rather avascular.

1. Tumour vessels and so-called vascular lakes. In 8 highly vascularized nodules, the tumour appeared as a vascular sphere. When tumour vessels were completely filled by hepatic artery injection, some vessels were thin and tortuous, while others were irregular with dilatation and constriction. The diameter of the vessels was usually smaller in highly vascularized nodules than in poorly vascularized nodules. In the latter, dilated abnormal vessels, viz. "vascular lakes", lined with a single layer of endothelial cells were found.

In hypovascular nodules, when tumour vessels were filled by both the arterial and the portal injection, the vessels filled from the portal vein were much wider than those filled from the hepatic artery /25, 27/.

2. Peripheral part and centre of tumour. Usually the central portion of a tumour had fewer vessels than its periphery. In most nodules, Microfil of 2 colours could be seen in the peripheral part of the tumours, particularly in tumour nodules with a moderate or small number of vessels.

In metastases exceeding 5 mm in diameter, an avascular zone usually could be seen in the centre in most cases corresponding to a necrotic area. In a few cases, however, the histopathological examination disclosed that the avascular central part was not due to the necrosis /23/.

3. Structures adjacent to the tumour. Two types of vascular patterns could be discriminated in areas peripheral to the tumour nodule. Either sinusoids appeared congested and dilated or an avascular zone surrounded the periphery of the tumour. The avascular zone corresponded in histological sections to several plates of liver cells lying closely together with compressed sinusoids.

4. Connection between tumour vessels and vessels outside the tumour. Tumour vessels could be directly connected with a small branch of the hepatic artery or with several portal venules also branching to surrounding sinusoids /23, 25, 27/.

Small branches of the hepatic artery along with branches of the portal vein could also be observed entering the tumour together and participating in the formation of tumour vessels. Sometimes, tumour vessels arose from an isolated branch of the portal vein extending into the tumour nodule /25/.

An avascular or hypervascular zone observed on CT in connection with contrast enhancement may be explained by the varied appearance of the structures adjacent to the metastasis /24/.

Experimental investigation in rats /13/. Coeliac angiography was successfully performed in 16 rats (4 rats in the control group and 12 rats in the embolization group) and revealed tumours in 13 (2 rats in the control group and 11 rats in the embolization group).

In the peripheral part of the tumour, encircling vessels, which originated from a branch of the hepatic artery, covered the entire tumour surface and formed an abnormal vascular network. Thus, the size and shape of the tumour was demarcated by the tumour vessels. The main feeding branch to the tumour was dilated and tortuous. The arrangement of tumour vessels in the tumour was bizarre.

During the capillary phase of the angiography, usually a rim of contrast accumulation could be seen in the periphery of the tumour. In the central part of the tumour, vessels were rather sparse. Occasionally, pools or lakes of contrast medium could be seen. Usually, however, an avascular area was observed in the centre of the tumour.

Postembolization angiography disclosed that peripheral occlusion of the hepatic artery was obtained in 6 rats after ethanol and proximal occlusion in 4 rats (1 after receiving ethanol and 3 after receiving gelfoam). No tumour vessels could be discerned in the tumour.

The livers were perfused with Microfil in all 20 rats and the results are shown in Table 3.

- A. Control group. Adjacent to the main tumour nodule, single small tumour nodules, measuring less than 1 mm in diameter, could be occasionally found. In these very small tumour nodules, irregular tumour vessels or vascular lakes could be seen. With increasing size of the tumour, encircling vessels from both arterial and portal circulations covered the tumour surface.

In some rats, tumour vessels in the periphery or vascular lakes in the centre originated solely from the portal circulation. As the tumour nodule reached the size of 1 cm in diameter, no extensive filling of tumour vessels in the central part of the tumour by the portal route was observed. This was quite different from the findings in cadaver liver metastases in man.

Most of the tumours ranging in size between 1 and 2.5 cm had an avascular area in the central portion because of necrosis.

- B. Embolization group. The vascular patterns of the tumours in the embolization group were the same as in the control group except more frequently tumour lakes were filled by the portal injection. When the portal vein was first injected with Microfil, tumour lakes filled from the portal vein were obtained in one case in the control group (20 %), but in 2 cases in the gelfoam group (50 %), and in 6 cases in the ethanol group (85 %).

Angiographic appearance of primary hepatic carcinoma /26/. Angiography was performed in 94 patients and in 82 of these a diagnosis of tumour was obtained. Histopathological diagnosis of hepatic cell carcinoma was confirmed in 38 operated patients with a positive angiographic diagnosis. In the remaining 44 patients, the diagnosis was supported by clinical data. Of the 12 patients who had negative angiography, 4 were operated on and in 3 a hepatocellular carcinoma was found. The remaining 8 patients with normal angiography were carefully studied and followed. Hepatic carcinoma was finally excluded clinically.

In 65 patients (79 %) tumour vessels appeared haphazardly distributed with an irregular lumen in a spherical tumour. Frequently, the feeding vessels were dilated and distorted. Tumour vessels were also observed in tumour only 1 - 2 cm in diameter.

Accumulation of contrast medium in the tumour ("tumour stain") was observed in 68 patients (83 %) during the capillary phase of angiography. The tumour stain had a higher density than the surrounding hepatic parenchyma, clearly demonstrating the tumour. Small hepatic carcinomas opacified distinctly as solitary spherical lesions, whereas the larger ones were slightly lobulated. This was particularly well shown when common hepatic angiography was performed. Cases with abundant tumour vessels in the arterial phase usually showed tumour stain in the capillary phase. Rarely was tumour stain obvious if there were only a few tumour vessels in the arterial phase. In larger tumours, because of central necrosis, tumour stain was more apparent at the periphery. The central portion showed filling defects or irregular density.

Pooling of contrast medium appeared in 44 patients (54 %) during the arterial phase and disappeared slowly, remaining visible after the arteries emptied.

Arterial stretching, displacement, and distorsion (46 patients, 56 %) were commonly seen in primary hepatic carcinoma. The larger the tumour, the more conspicuous they were.

Vascular encasement was observed in 38 patients (46 %). Typically, the arteries showed irregular serrations and suggestions of rigidity when they were encased by the tumour.

Arterioportal shunting was observed in 24 patients (29 %). The portal branches were present during the arterial phase most often in the periphery of the liver.

A tumour thrombus in the portal vein was present in 17 patients (21 %). When the portal vein and its main branches were involved by tumour thrombi, filling

defects and numerous small vascular structures were filled with contrast medium and arranged in parallel fashion. This observation was made in 6 of our patients.

The angiographic findings reported above did not appear alone. Usually several vascular abnormalities appeared simultaneously. Since most hepatic carcinomas developed on the basis of liver cirrhosis, tortuous hepatic arteries because of liver shrinkage were a common observation.

Discussion

The role of the portal vein in the nourishment of the hepatic tumour. It has been demonstrated in Microfil studies of experimental animals that small liver tumours receive their blood supply from both the hepatic artery and the portal vein /2, 13/. Using Microfil perfusion in rats, we also observed that encircling tumour vessels from both the hepatic artery and the portal vein covered the tumour surface and entered the tumour. Tumour vessels could be filled with Microfil exclusively by portal injection. The number of tumour vessels originating from the portal vein was increased particularly after ethanol embolization. The reason for this may be that peripheral arteries were more effectively occluded by the ethanol. Since experimental studies have shown that tumour growth takes place mainly in the periphery of the tumour, HONJO and MATSUMARA /18/ considered that tumour cells in the central area do not participate in the actual growth of the tumour.

The high nutritional demands in the periphery of the tumour may explain the supply both from the hepatic artery and the portal vein /18, 30/. The frequency of tumour lakes filled by the portal injection was much higher in the embolization group than in the control group. A possible explanation of this may be that after arterial embolization the periphery of the tumour becomes a low-pressure and low-oxygenated field. Consequently, there is a high demand for nutrition from all existing vessels in the vicinity /20/.

The central part of metastases larger than 5 mm was often avascular, which in most cases represented necrosis at histopathological examination. There was not complete correlation, however, which probably can be attributed to the technique. Thus, the Microfil could not be forced into all vessels because counterpressure was not applied during the manual injection.

Previous studies have shown that arterioportal communications exist at 3 levels within the liver /6, 8/: 1/ the peribiliary arterial plexus; 2/ the vasa vasorum of the portal vein; and 3/ direct arterioportal connections in the sinusoids. Therefore, arterioportal communications increase the oxygen saturation in the portal vein, which could favour tumour growth in the periphery.

That the tumour also receives its blood supply from the portal vein was demonstrated not only in the experimental animals, but also in man. We found that the tumour nodules can receive their blood supply from small portal venules bifurcating into normal sinusoids around the tumours and into the tumour vessels /25, 27/.

In a post-mortem study, we obtained extensive filling of tumour vessels by portal vein injection /27/. In the post-mortem specimen it may be due to an artefact. Thus, Microfil injected only or first into the portal vein may pass in a reverse direc-

tion through the arterioportal connections and then via arterial branches fill the tumour vessels. However, the presence of tumour vessels stained from the portal vein when the hepatic artery was the first to be injected or when simultaneous injections were performed speaks definitely in favour of the presence of a direct portal venous supply. Another fact in favour of a portal venous supply is the observation of large portal branches entering the tumour nodules. Based upon our findings /13, 25, 27/, there is therefore reason to believe that after the hepatic artery occlusion the role of the portal blood supply of a liver tumour becomes more important for its nourishment.

Intraportal infusion of 5-Fu or portal vein ligation has been tried in the treatment of liver tumours. Improved survival has been reported with portal infusion of 5-Fu compared with histologically untreated patients /38/. Using portal vein ligation, significant palliation has been obtained in some patients /19/.

In view of the dual blood supply of liver tumours, it is reasonable to suggest that the approach for improved treatment of hepatic neoplasms in the future should not only be via the hepatic artery but also via the portal vein.

Clinical significance of Microfil study for the understanding of the findings at angiography and CT. The Microfil perfusion technique has been widely used in the study of the microvascular patterns of various organs /9, 11, 16, 32/. It can also be used to study the microvascular architecture and blood circulation of liver tumours. Three-dimensional aspects of the microvascular architecture can be obtained in this way. A correlation between the Microfil preparations and the histological sections of hepatic tumours may explain findings at angiography and contrast enhancement CT, such as tumour stain, tumour lakes, and a peripheral high- or low-density ring around a tumour.

Tumour stain is a common finding in the angiographic capillary phase of a primary liver carcinoma (80 %), as well as of hypervascular liver metastases. Tumour stain is not well understood. REUTER and REDMAN /31/ considered that tumour stain might be contrast accumulation in the interstitial spaces of the tumour or within many small vascular channels or both. From our Microfil study of hypervascular metastatic nodules, the tumour appeared as a vascular sphere and tumour vessels were very thin and irregular. Therefore, when contrast medium passes through these small vessels, the flow probably is impeded, and thus the tumour remains stained when the normal liver parenchyma is cleared. The reduced flow would also permit some of the contrast medium to pass into the interstitial spaces.

Also tumour lakes are incompletely understood. These lakes might be areas of necrosis or vascular degeneration /3/. A correlation between Microfil vascular preparations and histological sections of the same metastases showed that tumour lakes were in fact dilated abnormal vessels lined with a single layer of endothelial cells.

At angiography or CT, a high- or low-density ring could be seen in the periphery of the tumour; the former being more common than the latter /28, 39/. From our study /23, 27/ the peripheral high-density ring was found to be congested and dilated sinusoids outside the tumour. The high-density ring could also be produced by a hypervascular tumour with a necrotic centre. A low-density ring around a tumour was determined histologically to be several layers of liver cells with compressed, empty sinusoids or fatty degeneration of liver cells /5/.

Summary and conclusions

Three different investigations were performed to study the vascularity of liver tumours.

- A. Sixteen human cadavers with liver metastases were examined using the Microfil perfusion technique. In addition, correlation study between Microfil preparations and histological sections was carried out in 23 specimens from 12 of the cadavers.
- B. Selective arteriography was performed in 94 cases clinically diagnosed or suspected to have hepatic carcinoma.
- C. Selective angiography and embolization were performed in 20 rats with implanted liver tumours. The following conclusions were arrived at:
 - 1. Most metastases had both an arterial and a portal blood supply, although the arterial supply prevailed. The same type of metastases could be filled either from the hepatic artery or from the portal vein.
 - 2. The vascular patterns of the metastases varied in different livers, but nodules from the same liver had the same type of tumour vessels irrespective of tumour size. With increasing size, the number of tumour vessels decreased in the centre of the tumour. The Microfil preparations corresponded well with the histopathological sections in most cases.
 - 3. In an experimental study in rats, filling of tumour lakes from the portal vein was seen more often in embolized animals than in controls, indicating the potential role of portal blood in nourishing the tumour.
 - 4. In the view of the dual blood supply of hepatic tumours, there is reason to believe that the approach for treatment of liver tumours in the future should not only be via the hepatic artery but also via the portal vein.
 - 5. The observations made in the Microfil preparations and the histological sections of hepatic tumours may explain some of the findings at angiography (distribution of tumour vessels, vascular lakes, central avascularity) and CT (hyper- or hypodensity of peripheral ring).

REFERENCES

1. ACKERMAN N.B.: Experimental studies on the circulatory dynamics of intra-hepatic tumor blood supply. *Cancer* 29 (1972), 435
2. ACKERMAN N.B.: The blood supply of experimental liver metastases. IV. Changes in vascularity with increasing tumor growth. *Surgery* 75 (1974), 589
3. ACKERMAN N.B. and HECHMER P.A.: The blood supply of experimental liver metastases. V. Increased tumor perfusion with epinephrine. *Amer J Surg* 140 (1980), 625
4. ACKERMAN N.B., LIEN W.M., KONDI E.S. and SILVERMAN N.A.: The blood supply of experimental liver metastases. I. The distribution of hepatic artery and portal vein blood to "small" and "large" tumors. *Surgery* 66 (1969), 1067
5. ANGRES G., CARTER J.B. and VELASCO J.M.: Unusual ring in liver cell adenoma. *Amer J Roentgenol* 135 (1980), 172
6. BOOKSTEIN J.J., CHO K.J., DAVIS G.B. and DAIL D.: Arterioportal communications. Observations and hypotheses concerning transsinusoidal and trans-vascular types. *Radiology* 142 (1982), 581
7. BREEDIS C. and YOUNG G.: Blood supply of neoplasms in the liver. *Amer J Pathol* 30 (1954), 969
8. CHO K.J. and LUNDERQUIST A.: Experimental hepatic artery embolization with gelfoam powder. *Invest Radiol* 18 (1983), 189
9. CHO K.J. and LUNDERQUIST A.: The peribiliary vascular plexus: The micro-vascular architecture of the bile duct in the rabbit and clinical cases. *Radiology* 147 (1983), 357
10. CHUANG V.P.: Hepatic tumor angiography. A subject review. *Radiology* 148 (1983), 633
11. DAVIDSON J.W. and HOBBS B.B.: The lymphatic microcirculatory spaces in lymph nodes during an immune response. *Invest Radiol* 9 (1974), 82
12. EKELUND L., HENRIKSON H., OLIN T. and SJÖGREN H-O.: Angiography in hepatic cysts and tumors in the rat. *Invest Radiol* 9 (1974), 396
13. EKELUND L., LIN G. and JEPSSON B.: The blood supply of experimental liver tumors following intraarterial embolization with gelfoam powder and absolute ethanol. *Cardiovasc Intervent Radiol* (Acc for publication) (III)
14. EKELUND L. and OLIN T.: Catheterization of arteries in rats. *Invest Radiol* 5 (1970), 69
15. EKELUND L., STIGSSON L., JONSSON N. and SJÖGREN H-O.: Transcatheter arterial embolization of normal liver and experimental hepatic tumors in rats. *Acta Radiol Diagnosis* 18 (1977), 641

16. HASE T.: Observations on microcirculatory architecture of the rat liver. *Anat Rec* 156 (1966), 157
17. HEALY J.E.: Vascular pattern in human metastatic liver tumors. *Surg Gynecol Obstet* 120 (1965), 1187
18. HONJO I. and MATSUMARA H.: Vascular distribution of hepatic tumors. Experimental study. *Rev Int Hepatol* 15 (1965), 681
19. HONJO I., SUZUKI T., OZAWA K., TAKASAN H., KITAMURA O. and ISHIKAWA T.: Ligation of a branch of the portal vein for carcinoma of the liver. *Amer J Surg* 130 (1975), 296
20. HOSOKI T., CHATANI M. and MORI S.: Dynamic computed tomography of hepatocellular carcinoma. *Amer J Roentgenol* 139 (1982), 1099
21. KIDO C.: Hepatic angiography of experimental transplantable tumor. *Invest Radiol* 5 (1970), 341
22. LIEN W.M. and ACKERMAN N.B.: The blood supply of experimental liver metastases. II. A microcirculatory study of the normal and tumor vessels of the liver with the use of perfused silicone rubber. *Surgery* 68 (1970), 334
23. LIN G., BOIJSSEN E., HÄGERSTRAND I. and LUNDERQUIST A.: Microvasculature architecture of small liver metastases in man. A correlation between Microfil vascular preparations and histological sections. *Invest Radiol* (Acc for publication) (IV)
24. LIN G., GUSTAFSON T., HÄGERSTRAND I. and LUNDERQUIST A.: Low density ring in liver metastases on CT. *J Computer Assist Tomogr* (Acc for publication) (V)
25. LIN G., HÄGERSTRAND I. and LUNDERQUIST A.: Portal blood supply of liver metastases. *Amer J Roentgenol* (Acc for publication) (II)
26. LIN G., HAN X., JIN G., RONG D-S., WANG S., WANG G. and SHEN X.: Selective angiography in diagnosing primary hepatic carcinoma. *Chinese Med J* 95 (1982), 667 (VI)
27. LIN G., LUNDERQUIST A., HÄGERSTRAND I. and BOIJSSEN E.: Post-mortem examination of the blood supply and vascular pattern of small liver metastases in man. *Surgery* (Acc for publication) (I)
28. MARCHAL G.L., BAERT A.L. and WILMS G.E.: CT of noncystic liver lesions. Bolus enhancement. *Amer J Roentgenol* 135 (1980), 57
29. NILSSON L.A.V. and ZETTERGREN L.: Blood supply and vascular pattern of induced primary hepatic carcinoma in rats. A microangiographic and histologic investigation. *Acta Pathol Microbiol Scand* 71 (1967), 179

30. NILSSON L.A.V. and ZETTERGREN L.: Effect of hepatic artery ligation on induced primary liver carcinoma in rats. Preliminary report. Acta Pathol Microbiol Scand 71 (1967), 187
31. REUTER S.R. and REDMAN H.C.: Gastrointestinal Angiography. 2nd ed. W.B. Saunders, Philadelphia (1977)
32. REYNOLDS D.G.: Silicone rubber technique for microvascular study. Lab Mgmt 6 (1968), 24
33. ROGERS W., EDLICH R.F., LEVIS D.V. and AUST J.B.: Tumor blood flow: I. Blood flow in transplantable tumors during growth. Surg Clin North Amer 47 (1967), 1473
34. SOO C-S., CHUANG V.P., WALLACE S., CHARNsangAVEJ C. and CARRASCO H.: Treatment of hepatic neoplasm through extrahepatic collaterals. Radiology 147 (1983), 45
35. STEELE G. Jr., and SJÖGREN H-O.: Cross-reacting tumor associated antigen(s) among chemically induced rat colon carcinomas. Cancer Res 34 (1974), 1801
36. STIGSSON L., EKLUND L., JONSSON N. and SJÖGREN H-O.: Transcatheter arterial embolization of experimental hepatic tumors in the rat. Acta Radiol Diagnosis 20 (1979), 422
37. STRIDBECK H., LÖRELIUS L.E. and PIRTLE T.E.: Distal embolization of the hepatic artery in pigs. Cardiovasc Intervent Radiol (1983). Acc for publ.
38. TAYLOR J.: Cytotoxic perfusion for colorectal liver metastases. Brit J Surg 65 (1978), 109
39. WOOTEN W.B., BERNARDINO M.E. and GOLDSTEIN H.M.: Computed tomography of necrotic hepatic metastases. Amer J Roentgenol 131 (1978), 839

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POST-MORTEM EXAMINATION OF THE BLOOD SUPPLY
AND VASCULAR PATTERN OF SMALL LIVER
METASTASES IN MAN

GUI LIN, ANDERS LUNDERQUIST, INGA HÄGERSTRAND and ERIK BOIJSEN

Abstract

Thirteen human cadavers with liver metastases were examined. Microfil was injected into the portal vein and hepatic artery. The liver metastases were examined under dissecting microscope and their vascular supply and patterns were registered. It was found that most metastases had both arterial and portal supply even if the arterial dominated. In one liver where the portal vein of one lobe and the hepatic artery of the other was injected extensive filling of tumor vessels were observed in both lobes, i.e. the same kind of metastases could be filled either from the hepatic artery or from the portal vein. It is suggested that the findings could be of great importance in planning treatment of patients with liver metastases.

Key words

Liver metastases, Tumor vessels, Vascular supply, Hepatic artery, Portal vein

The angiographic diagnosis of hepatic metastases has been discussed in many reports. A systematic analysis of the vascular supply of various types of hepatic tumors is nevertheless not available. Variations in angiographic technique but also the limited resolution available in clinical work preclude a detailed evaluation of the vascular supply of hepatic tumors. Both in order to understand the varying clinical angiographic pattern of hepatic metastases and to institute treatment it is important to know how the tumors are nourished. Most research work done to define the blood supply of hepatic metastases has been performed in animals /1, 2, 3, 4, 5, 6, 7/. Only few reports on human cadavers are available /8, 9/. The information obtained has been controversial.

The purpose of the present study was therefore to define the vascular pattern as well as the blood supply of the small and medium-sized liver metastases by injecting silicone rubber into the hepatic artery and portal vein of human cadavers. The main purpose was to find a proper method for cytotoxic administration.

Material and methods

Thirteen human livers with metastases of various sizes and origin were examined at autopsy. A total of 101 metastases measuring less than 1 cm in diameter were obtained for special examination. The metastases originated from carcinoma of the breast (4), lung (3), colon (2), prostate (2), pancreas (1), and gallbladder (1) altogether 8 males and 5 females (age range 35 - 85 years).

After the whole liver had been removed from the fresh cadaver, the portal vein and the hepatic artery were exposed, cannulated with a polyethylene catheter, and injected with Microfil^R (Canton Bio-Medical Products, Boulder, Colorado, USA) until the vessels appeared to be well-filled. Thus, when Microfil was seen to flow from the hepatic veins and when small vascular structures could be well demonstrated on the surface of the liver the infusion was stopped. The injection was performed manually. The volume of Microfil used depended on the size of the liver. Generally,

30 - 40 ml and 40 - 50 ml were enough to perfuse the hepatic artery and portal vein, respectively.

White or yellow Microfil (MV-112 or MV-122) was usually first injected into the portal vein, then orange Microfil (MV-117) was injected into the hepatic artery of the same lobe (Table 1). If the portal vein and the hepatic artery were perfused subsequently in the same liver lobe (9 livers, cases 4 - 12) additional curing agent was added to the first injected material to accelerate the curing process. The second injection was performed 2 - 3 hours later to prevent mixing of the two colors. In one liver Microfil was first injected into the hepatic artery (case 12) and in another liver simultaneous injection was made into the hepatic artery and portal vein of the same lobe (case 13). In one liver the portal vein was injected in one lobe and the hepatic artery in the other (case 1). In 2 livers only single injections were made into the hepatic artery (case 2) and portal vein (case 3), respectively.

After completed injections the specimens were kept in a refrigerator over night. The liver was then cut and pieces containing different sizes of small metastatic nodules surrounded by normal parenchyma were selected for the clearing procedure. This was accomplished by immersing the specimens into ethanol of increasing concentrations, 1 - 2 days in each 25 %, 50 %, 75 %, 95 % and 99.5 % of ethanol. Finally, the specimens were placed in methylsalicylate. When the oil had penetrated the tissue it became transparent and could consequently be examined under the stereomicroscope.

Six of the specimens were later treated with decreasing concentrations of ethyl alcohol before they were fixed in formaline for histologic examination.

Results

A total of 101 small metastases were examined 27 of which were less than 3 mm, 26 were 3 - 5 mm, and 38 were 5 - 10 mm in diameter. The results are presented according to the type of vascular perfusion observed in the experiments, i.e. if the tumor showed pure arterial, portal or mixed arterial and portal filling. Also the vascular architecture of the tumors was interpreted.

Tumor perfusion exclusively from the hepatic artery was observed in 12 tumor deposits examined in 4 cases in which the portal vein and hepatic artery were injected. In the same 4 cases both arterial and portal perfusion was observed in another 18 tumor deposits examined. In the larger tumors the arterial supply dominated.

Only hepatic artery perfusion was observed in 4 tumor nodes of a total of 61 examined in which the portal vein was first injected followed by hepatic artery injection, while it was seen in 5 out of 10 nodules in which hepatic artery was the first vessel to be injected in the same lobe (Table 1, case 12).

The following different vascular patterns were observed: The tumor vessels formed a rich network of which some vessels were thin, normally tapering, while others were irregular with abrupt dilatation and narrowing (Fig. 1). Also the very small metastases (about 1 mm) had a similar pattern. Sometimes the tumor vessels were connected with irregular vessels from sinusoids in the surrounding liver parenchyma (Fig. 2). In some cases the sinusoids adjacent to the metastases appeared congest-

Table 1. Distribution of tumor perfusion observed in 101 small metastases,
PV-portal vein, HA-hepatic artery.

Case No.	Carcinoma of	Injection		Tumor perfusion			Total
		First	2nd	HA	PV	both	
1	Breast right lobe left lobe	PV	HA	6	4		10
2	Colon	HA		2			2
3	Prostate	PV			6		6
4	Gallbladder	PV	HA	2		3	5
5	Lung	PV	HA	2		1	3
6	Lung	PV	HA			24	24
7	Lung	PV	HA			3	3
8	Pancreas	PV	HA			5	5
9	Colon	PV	HA			7	7
10	Breast	PV	HA			2	2
11	Breast	PV	HA			12	12
12	Breast	HA	PV	5		5	10
13	Prostate	Simultaneously HA, PV		3		9	12
				20	10	71	101

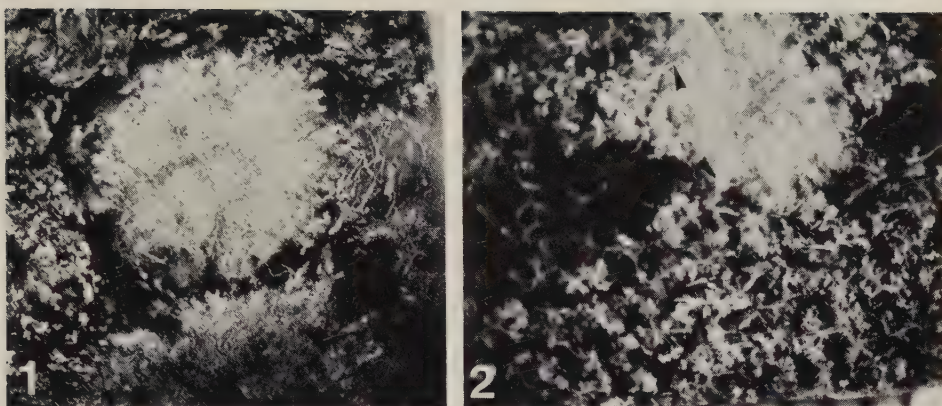


Fig. 1. Case 1. Seven mm metastasis from breast carcinoma. Only hepatic artery injected. Richly vascularized metastatic nodule. Mostly normal tapering vessels, but irregular vessels appear in peripheral part of the tumor. The avascular zone surrounding the tumor contains compressed sinusoids and liver cells, and non-filled portal veins. Compare with Fig. 7 which is the same case, but with portal vein injection only.

Fig. 2. Case 5. Richly vascularized 4 mm metastasis from lung carcinoma, supplied mainly from the hepatic artery but also from portal vein. Originating from the sinusoid vessels filled from the portal vein penetrate the tumor in the periphery (arrow heads). Lower vascularization in the center of the tumor.

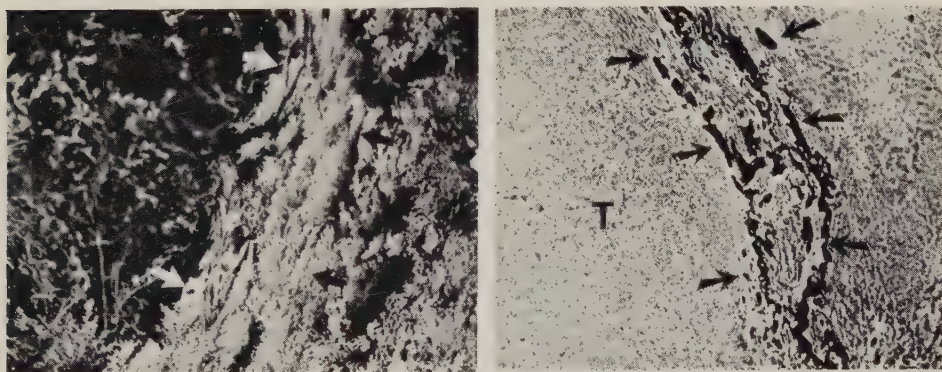


Fig. 3. Case 4. Metastasis from carcinoma of the gallbladder. A/ Congested sinusoids peripheral to the tumor (arrows). B/ Histologic examination shows the congested sinusoids partly filled with Microfil (black) peripheral to the tumor (T). (x 85).

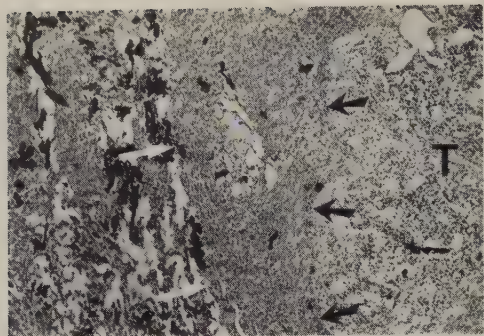


Fig. 4. Case 1. Carcinoma of the breast. The same case as in Fig. 1. Histologic examination shows compressed liver cell plates (arrows) peripheral to the tumor (T). Very few vessels are seen within this zone. (x 85).

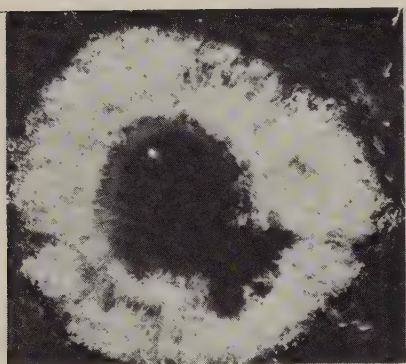


Fig. 5. Case 5. A/ Injection first into portal vein followed by injection into the hepatic artery. Tumor supplied mainly by the hepatic artery (gray), but single radiating vessels in connection with portal vein observed in the periphery (white). Avascular central zone represents tumor necrosis. B/ Histologic examination of the same tumor shows a necrotic zone in the center of the tumor. (x 7).

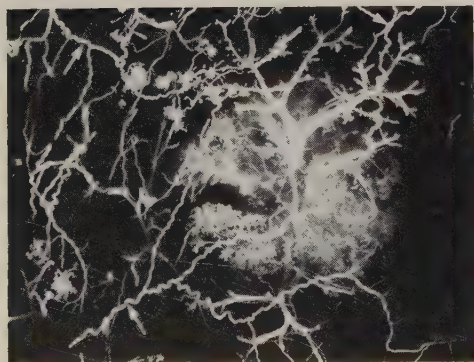


Fig. 6. Case 10. Medium vascularized 6 mm metastasis from breast carcinoma. The tumor is situated beneath the capsule of the liver and derives its blood supply from dilated capsular arteries originating from the diaphragmatic artery and the hepatic artery.

ed and dilated (Fig. 3). In some the vascular sphere was surrounded by an avascular zone (Fig. 1). On histologic examination this avascular zone proved to be plates of liver cells with compressed empty sinusoids (Fig. 4). A mixture of these patterns could be seen peripheral to the same tumor nodule.

In metastases larger than 5 mm in diameter an avascular zone could be observed in the center (Fig. 5). Metastases situated beneath the capsule of the liver were supplied by dilated capsular arteries originating from the diaphragmatic arteries (here filled in retrograde direction from hepatic arteries), as well as by the hepatic artery (Fig. 6).

Tumor perfusion exclusively from the portal vein was not observed in any of the cases where both the portal vein and the hepatic artery were injected. In 2 cases (Nos. 1 and 3) where only the portal vein was injected tumors studied showed extensive filling of tumor vessels (Fig. 7).

The tumor vessels had the same appearance as described when the nodules were filled from the hepatic arteries. This was particularly well demonstrated in the liver where the hepatic artery was perfused in one lobe and the portal vein in the other (case 1, Figs. 1 and 7).

Perfusion of tumor vessels from both the hepatic artery and the portal vein was observed in 71 of 83 tumors examined (cases 4 to 13). Vessels in the periphery of the tumors were usually filled with Microfil of two colors (Fig. 8). As a rule, the tumor vessels filled with white color (portal vein) were more irregular and wider than those filled with the orange color (from the hepatic artery). A portal branch and a branch of the hepatic artery sometimes passed together into the metastatic nodule where they branched into tumor vessels (Fig. 9). Using simultaneous injection into the hepatic artery and portal vein (case 13) the mixture of Microfil of two colors could be seen in irregular tumor vessels. Occasionally, a branch of the portal vein was surrounded by a metastatic nodule (Fig. 10). Most often, however, the portal vein branches ended abruptly at the tumor periphery and were displaced by the mass. Arterioportal connections were repeatedly observed.

In the case of breast carcinoma (case 1) in which the portal vein of one lobe and the hepatic artery of the other was injected separately, extensive filling of tumor vessels was observed in both lobes - in one from the hepatic artery, in the other from the portal vein.

The vascular pattern of the metastases varied in different livers but nodules from the same liver had the same type of tumor vessels, irrespective of tumor size. In nodules less than 3 mm abnormal vessels were present throughout the tumor. With increasing size the number of tumor vessels decreased in the center of the tumor (Fig. 5). Sometimes a vascular lake could be observed in the center of the tumor (Fig. 11).

Correlation between the Microfil vascular preparations and histological sections of the same metastases was made in 6 specimens. As mentioned previously, an avascular zone could often be observed peripheral to the metastatic nodule (Fig. 1), and corresponded to plates of liver cells with compressed sinusoids (Fig. 4). A zone of dilated vessels peripheral to the tumor corresponded to deformed and dilated sinusoids (Fig. 3).

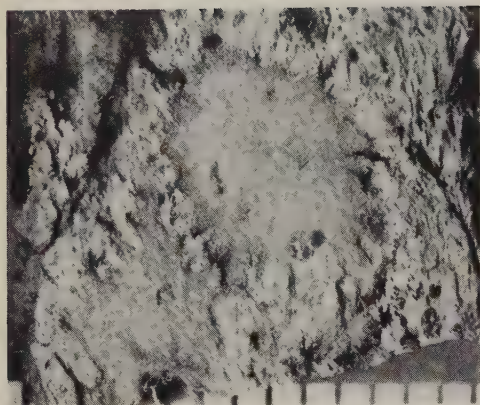


Fig. 7. Case 1. Four mm tumor nodule is supplied exclusively from the portal vein which was the only vessel injected in this part of the liver. Observe there is no avascular zone surrounding the nodule. The tumor vessels have the same appearance as in Fig. 1.

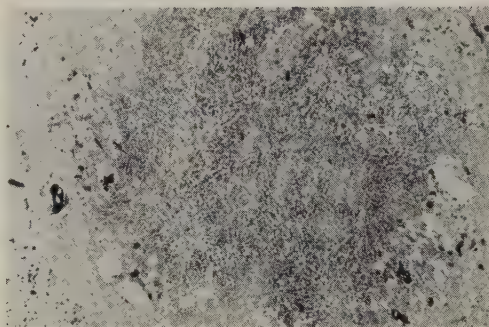


Fig. 8. Case 11. Metastatic nodule from breast carcinoma. A/ Peripheral part of the tumor nodule is perfused with Microfil of two colors. The most distended tumor vessels are filled from the portal vein (white). Vessels appearing gray are filled from the hepatic artery. Avascular center in tumor suggests necrosis. B/ Histologic section. Dilated vessels in the periphery of the tumor nodule. No central necrosis. The black material (Microfil) sometimes remains inside the vessel but in most places removed during the preparation of the slice. (x 25).

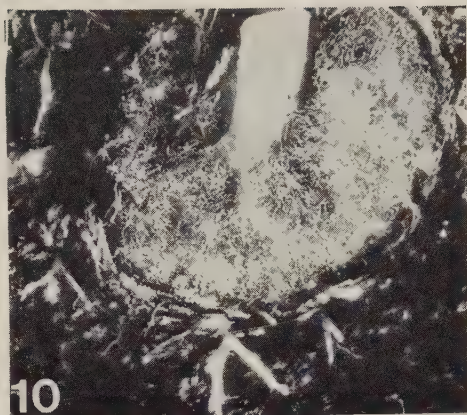


Fig. 9. Case 8. Three mm metastasis from pancreatic carcinoma, supplied from both hepatic artery and portal vein. Tumor vessels arising from the portal vein (curved arrow) are more irregular and wider than those from the hepatic artery (white arrow).

Fig. 10. Case 6. Hypervascular metastatic nodule from lung carcinoma. A branch of the portal vein is surrounded by the tumor nodule.

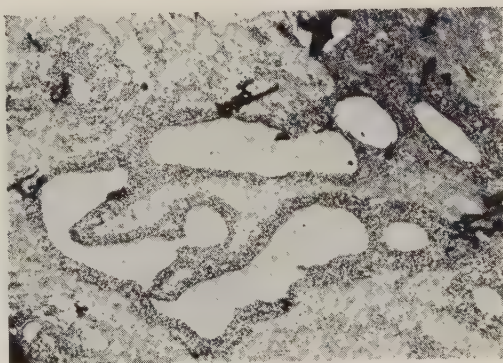
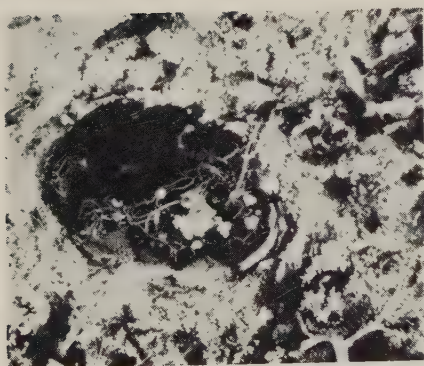


Fig. 11. Case 9. A/ Hypovascular 5 mm metastasis from colon carcinoma. Clusters of vessels originating from the portal vein are forming vascular lakes and a few small arterial branches are seen. B/ Histologic section. The vascular lakes within the tumor are well demonstrated. (x 85).

There was a good correlation between the number and appearance of vascular structures in the casts and the histological sections. Large vascular lakes could be identified in both types of preparations (Figs. 11 A and B). However, an area without vessels at Microfil examination did not necessarily correspond to a necrotic area at histologic examination even if so usually was the case. In a few specimens no necrosis could be observed in the histological section which probably could be explained by an incomplete Microfil perfusion (Fig. 8).

Discussion

Microfil injection into the hepatic artery and portal vein to study human livers with metastases has previously not been presented. From experimental studies in rats it is evident that the tumor supply can be demonstrated with this technique /3/. It should, however, be clear that the experimental model by ACKERMAN and his group (1969) did not permit a maximum filling of all hepatic vessels, and therefore, the tumor vessels would be incompletely filled. This became obvious after the injection of epinephrine into the aorta prior to the Microfil injection in the living animals /10/. Also the injections of Microfil into the hepatic artery and portal vein in cadavers give incomplete information of all vessels and therefore artifacts must be expected, which was also found in our series when compared to histologic sections. The limitations of the present method should thus be born in mind when evaluating the results.

The experimental studies have shown that small liver tumors receive their blood supply from both the hepatic artery and portal vein /4, 5, 6, 9, 12/. The vascularity of experimental liver tumors is at least partly dependent on the size and growth of the tumors and it appears to be a continually changing phenomenon /1/. Thus, in experimental tumors in rats, the arterial supply increased relative to the supply from the portal vein when the tumor became larger. In tumors less than 1 mm ACKERMAN did not observe any circulation at all to the tumors. The present study, however, shows that metastases of 1 mm in diameter have a rich vascular supply from the hepatic artery. It is obvious that the demonstrated supply varied with the injection technique used and that the same vessels of a small tumor may be filled from the portal vein as well.

Previous studies have shown that there exist arterioportal communications at 3 levels within the liver /7/: 1. the peribiliary arterial plexus anastomoses with the portal vein; 2. the vasa vasorum of the portal vein has direct connection with the portal vein, and 3. there are direct arterio-portal connections in the sinusoids. The presence of these arterio-portal anastomoses could explain our observations in human livers that small metastases have a portal supply both from the peripheral portal branches via the sinusoids and via small arterial branches.

When the tumor nodule grows larger we believe that peripheral portal branches become compressed and obliterated. The venous participation of the supply is reduced and to maintain the nutrition of the tumor the more resistant artery dilates. There are, however, still connections between the hepatic artery and portal vein which may explain a partial portal take-over if the artery becomes occluded. The therapeutic effect of ligation of the hepatic artery in patients with hepatic metastases is therefore ineffective for two reasons. First, the collateral arterial circulation soon compensates the occlusive effect. Second, the intrahepatic arterio-portal connections take over.

In the treatment of liver metastases we therefore think it would be more effective to occlude peripheral branches of the hepatic artery and deliver the cytotoxic drug into the portal vein than to deliver the drug only into the hepatic artery.

REFERENCES

1. ROGERS W., EDLICH R.F., LEVIS D.V. and AUST J.B.: Tumor blood flow. I. Blood flow in transplantable tumors during growth. *Surg Clin North Amer* 47 (1967), 1473 - 1482
2. NILSSON L.A.V. and ZETTERGREN L.: Effect of hepatic artery ligation on induced primary liver carcinoma in rats. Preliminary report. *Acta Path Microbiol Scand* 71 (1967), 187 - 193
3. ACKERMAN N.B., LIEN W.M., KONDI E.S. and SILVERMAN N.A.: The blood supply of experimental liver metastases. I. The distribution of hepatic artery and portal vein blood to "small" and "large" tumor. *Surgery* 66 (1969), 1067 - 1072
4. LIEN W.M. and ACKERMAN N.B.: The blood supply of experimental liver metastases. II. A microcirculatory study of the normal and tumor vessels of the liver with the use of perfused silicone rubber. *Surgery* 68 (1970), 334 - 340
5. ACKERMAN N.B.: Experimental studies on the circulatory dynamics of intra-hepatic tumor blood supply. *Cancer* 29 (1972), 435 - 439
6. ACKERMAN N.B.: The blood supply of experimental liver metastases. IV. Changes in vascularity with tumor growth. *Surgery* 75 (1974), 589 - 596
7. KIDO C.: Hepatic angiography of experimental transplantable tumor. *Invest Radiol* 5 (1970), 341 - 347
8. BREEDIS C. and YOUNG G.: Blood supply of neoplasms in the liver. *Amer J Pathol* 30 (1954), 969 - 985
9. HEALY J.E.: Vascular pattern in human metastatic liver tumors. *Surgery* 120 (1965), 1187 - 1193
10. ACKERMAN N.B. and HECHMER P.A.: The blood supply of experimental liver metastases. V. Increased tumor perfusion with epinephrine. *Amer J Surg* 140 (1980), 625 - 631
11. HONJO I. and MATSUMARA H.: Vascular distribution of hepatic tumors. Experimental study. *Rev Int Hepat* 15 (1965), 681 - 690
12. ACKERMAN N.B., LIEN W.M. and SILVERMAN N.A.: The blood supply of experimental liver metastases. III. The effects of acute ligation of the hepatic artery or portal vein. *Surgery* 71 (1972), 636 - 641
13. NILSSON L.A.V. and ZETTERGREN L.: Blood supply and vascular pattern of induced primary hepatic carcinoma in rats. A microangiographic and histologic investigation. *Acta Pathol Microbiol Scand* 71 (1967), 179 - 186
14. CHO K.J. and LUNDERQUIST A.: Experimental hepatic artery embolization with gelfoam powder: Microfil perfusion study of the rabbit liver. *Invest Radiol* 17 (1982), 523

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PORTAL BLOOD SUPPLY OF LIVER METASTASES

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Short title: Portal blood supply

Abstract

Using Microfil technique the hepatic artery and the portal vein were injected in four human cadaver livers with metastases from various origin. Specimens were dissected under stereomicroscope and vessels supplying the tumor nodules were traced. In all cases tumor vessels could be filled from the portal side and in three of them the supplying portal branches were rather wide. The findings were correlated with the histologic sections.

Key terms

Liver - Liver metastases - Vascular supply - Portal vein

Controversy still exists whether liver tumors receive their blood supply exclusively from the hepatic artery /1/ or from both the hepatic artery and the portal vein /2 - 4/. The present study on human cadaver livers with metastases of various origin was performed in an attempt to identify the arterial and portal venous distribution to the tumors.

Material and methods

Four human livers with metastases from myeloma, breast, pancreas and lung were perfused with Microfil (Canton Bio-Medical Products, Inc., Boulder, Colorado, USA). The technique for this perfusion has been described previously /5/. In 3 cases white or yellow Microfil was injected into the portal vein and in 2 cases followed by orange Microfil into the hepatic artery. In one case the hepatic artery was first injected followed by injection into the portal vein.

After completed injection the specimen was kept in a refrigerator over night. Liver specimens containing metastatic nodules surrounded by normal parenchyma were dehydrated in increasing concentrations of ethanol and finally placed in methylsalicylate. When the specimens became transparent they were examined under stereomicroscope. Color photographs were taken of vascular structures of special interest and these specimens were then treated with decreasing concentrations of ethanol, embedded in paraffin, sectioned and stained with hematoxylineerythrosin, and sometimes with reticulin and/or collagen stains for histological examination.

Results

Portal venous branches could be traced in all 4 cases from normal liver parenchyma to the tumor nodules where they bifurcated.

In 2 cases abundant tumor vessels filled from the injected portal vein (Fig. 1). These tumor vessels were markedly wider than those in the surrounding liver parenchyma. In one of the cases where both the portal vein and the hepatic artery were injected the vessels filled from the portal side were wider and more irregular than those filled from the hepatic artery.

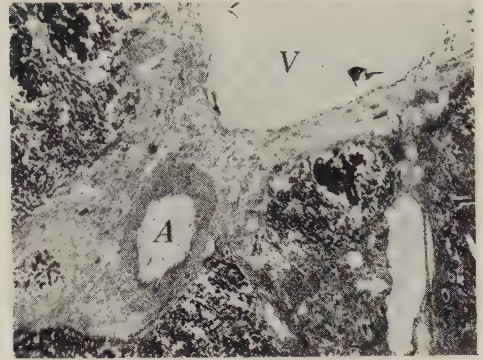


Fig. 1. Liver metastasis: from myeloma. A/ Tumor vessels are filled from the portal vein. Large branches arise from the portal vein and supply the tumor (arrows). V = portal vein. B/ Histologic section (x 35). A vessel (arrow) originates from the portal vein (V) and extends into the tumor. A = hepatic artery.

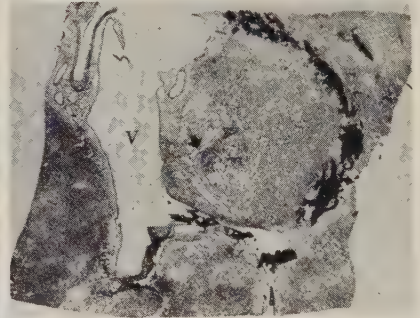


Fig. 2. Liver metastasis from breast carcinoma. A/ Tumor nodule mainly supplied by the hepatic artery (gray), but several vessels (arrows) from the portal vein (V) also supply the tumor. B/ Pathologic section well corresponds to the Microfil preparation in A. A vessel (arrow) from the portal branch (V) extends into the tumor. (x 8).

In the other 2 cases most of the tumor vessels were filled from the arterial side. However, in one of the cases a rather wide portal branch extended into the tumor where it bifurcated and was seen to connect with arterially filled tumor vessels (Fig. 2). In the other case portal venules surrounding the tumor bifurcated to normal sinusoids as well as to the tumor.

In no case Microfil injected into the portal vein was seen to pass over into arterial branches. The opposite was, however, a frequent finding with arterial injected Microfil passing into portal branches either over the biliary plexus or through tiny direct connections.

Histologic sections corresponded well to the Microfil preparations studied under the stereomicroscope.

Discussion

It has been demonstrated in experimental studies /2 - 3/ that small liver tumors receive the blood supply from both the hepatic artery and the portal vein but to our knowledge this has not been shown in humans. From observations in this limited number of specimens there is a strong evidence that liver metastases can derive their blood supply not only from the hepatic artery but also from the portal vein. It is of interest to note that liver metastases may be supplied by fairly large portal venous branches and not only from surrounding venules also feeding the sinusoids.

From experimental studies /3, 6/ it has been shown that the main growth of the liver tumors is in their periphery. Experimental studies /3, 7/ have also demonstrated that liver tumors can derive their blood supply from the portal vein after hepatic artery ligation. After the hepatic artery occlusion, the role of the portal blood supply of liver tumor becomes more important in the nourishment of the tumor.

Even if liver tumors receive their main blood supply from the hepatic artery, we believe that the role of the portal vein in the nourishment of the tumors should not be neglected. In the view of the double blood supply of liver metastases, we suggest that the approach for treatment of the liver tumors in the future should be not only via the hepatic artery but also via the portal vein.

REFERENCES

1. SOO C-S., CHUANG V.P., WALLACE S., CHARNSANGAVEJ C. and CARRASCO H.: Treatment of hepatic neoplasm through extrahepatic collaterals. *Radiology* 147 (1983), 45 - 49
2. ACKERMAN N.B., LIEN W.M., KONDI E.S. and SILVERMAN N.A.: The blood supply of experimental liver metastases. I. The distribution of hepatic artery and portal vein blood to "small" and "large" tumor. *Surgery* 66 (1969), 1067 - 1072
3. NILSSON L.A.V. and ZETTERGREN L.: Effect of hepatic artery ligation on induced primary liver carcinoma in rats. Preliminary report. *Acta Path Microbiol Scand* 71 (1967), 187 - 193
4. BREEDIS C. and YOUNG G.: Blood supply of neoplasms in the liver. *Amer J Pathol* 30 (1954), 969 - 985
5. LIN G., LUNDERQUIST A., HÄGERSTRAND I. and BOIJSEN E.: Post-mortem examination of the blood supply and vascular pattern of small liver metastases in man. Acc for publ in *Surgery*
6. HONJO I. and MATSUMARA H.: Vascular distribution of hepatic tumors. Experimental study. *Rev Int Hepat* 15 (1965), 681 - 690
7. LIEN W.M. and ACKERMAN N.B.: The blood supply of experimental liver metastases. II. A microcirculatory study of the normal and tumor vessels of the liver with the use of perfused silicone rubber. *Surgery* 68 (1970), 334 - 340

III

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THE BLOOD SUPPLY OF EXPERIMENTAL LIVER TUMORS FOLLOWING INTRAARTERIAL EMBOLIZATION WITH GELFOAM POWDER AND ABSOLUTE ETHANOL

LEIF EKELOUND, GUI LIN and BENGT JEPSSON

Abstract

Twenty rats with implanted liver tumor were studied. Following baseline angiography, the hepatic artery was embolized with gelfoam powder or ethanol in 12 rats while the remaining 8 rats comprised controls without embolization. Post-mortem Microfil perfusion was performed in all livers. Filling of tumor lakes from the portal vein was seen more often in embolized animals than in controls, indicating the potential role of the portal venous system in the supply of dearterialized hepatic tumors. The possible clinical implication of this finding is discussed.

Key words

Liver tumor - Embolization - Tumor lakes - Ethanol - Gelfoam powder - Portal circulation

It is generally believed that primary as well as secondary liver tumors receive their main blood supply from the hepatic artery /1 - 4/. Also recent articles presume that all hepatic tumors receive their blood supply exclusively from the hepatic artery /5/. In fact there is still some controversy about the role of the portal vein in the supply of these tumors /6 - 7/. After hepatic artery ligation, liver tumors can derive their blood supply from the portal vein, as demonstrated experimentally /8/. In the present study, special attention was paid to the analysis of vascular patterns and blood supply of experimental hepatic tumors shortly after intraarterial embolization with absolute ethanol or gelfoam powder.

Material and methods

Twenty Wistar rats weighing 200 - 250 g were used for the experiments. Under ether anesthesia, 0.1 ml of a standard cell suspension containing 1.0×10^6 cells of N-methyl-N-nitrosoquanidine induced transplantable adenocarcinoma /9/ was injected into the central lobe of the liver through a midline incision. Using this technique solitary liver tumors were induced and tumor "take" was 100 %.

Twenty liver tumors ranging in size 0.7 - 2.5 cm were studied. The rats were divided into 3 groups. The first group (control group) included 8 rats, the second group (gelfoam embolization group) 4 rats, and the third group (ethanol embolization group) 8 rats.

On the 9th to 19th day after inoculation, the rats were again anesthetized with ether and selective celiac or hepatic angiography (if possible) was performed according to the technique described previously /10-11/. For the celiac artery 0.3 to 0.5 ml of Isopaque Cerebral (Nyegaard A/S, Oslo, Norway) was injected manually and 0.2 to 0.3 ml for the hepatic artery.

A baseline angiogram was obtained in 4 of 8 rats in the control group without repeat angiography.

Table 1. Liver perfusion with Microfil in 20 rats with experimental hepatic tumors. (PV = portal vein, HA = hepatic artery).

Group	Animal No.	Injection		"Lake"	Lake filled by PV (%)
		First	Second		
Control	1	PV		-	
	2	PV		-	
	3	PV		-	
	4	PV		-	1/5 (20 %)
	5	HA		+	
	6	HA		+	
	7	HA		+	
	8	PV	HA	++	
Gelfoam	9	PV		+	
	10	PV	HA	-	2/4 (50 %)
	11	PV	HA	-	
	12	PV	HA	+	
Ethanol	13	PV		+	
	14	PV		+	
	15	PV		-	
	16	PV		+	
	17	HA		+	6/7 (85 %)
	18	PV	HA	++	
	19	PV	HA	++	
	20	PV	HA	++	

+ = lake at periphery of tumor

++ = lake at periphery as well as in center of tumor

Following baseline angiography, the celiac or hepatic artery was embolized with powder (Spongostan, Ferrosan Int., Denmark) or absolute ethanol in a group of 12 rats. The technique for powder embolization has been reported previously /12/. 0.1 - 0.15 ml of gelfoam powder (1 mg gelfoam powder in 4 ml of contrast medium) was injected under fluoroscopic control. The particle size of gelfoam powder mostly ranged from 0.005 to 0.2 mm. For ethanol embolization 0.2 - 1 ml of 95 % ethanol was injected very slowly by hand. In order to confirm occlusion of the hepatic artery, celiac angiography was repeated 15 minutes after embolization in 3 rats (gelfoam group) and in 7 rats (ethanol group), respectively.

Post-mortem Microfil (Canton Bio-Medical Products, Boulder, Colorado, USA) perfusion was performed in all 20 rats. Our technique for Microfil perfusion was similar to ACKERMAN's /13/. Different approaches for the liver perfusion were used (Table 1). At first, a catheter (OPP10, OD/ID 0.65/0.25 mm) was inserted into the abdominal aorta so that its tip reached just below the orifice of the celiac artery. The aorta was then ligated above and below the celiac artery. A similar catheter was also positioned in the portal vein. Vessels were perfused with Microfil manually until the vasculature was satisfactorily filled and Microfil flowed into the inferior vena cava. Orange Microfil (MV-117) was injected into the hepatic artery and yellow Microfil (MV-112) was injected into the portal vein. If both the portal vein and the hepatic artery were perfused subsequently in the same rat, yellow Microfil was first injected into the portal vein. Two hours later orange Microfil was injected into the aorta, and additional curing agent was added to yellow Microfil to accelerate the curing process and to prevent mixing of the two colors.

After complete curing of Microfil, the livers were subjected to a clearing procedure, by immersing them into ethanol of increasing concentrations, 1 - 2 days in each of 25, 50, 75, 95 and 99.5 % ethanol. Finally, the livers were placed in methyl salicylate. When the livers became transparent, radiograms were obtained using mammography technique. Because Microfil is radiopaque, radiograms can show the vascular architecture of the tumors and the liver parenchyma. The specimens were then examined and photographed under the dissecting microscope.

Five of the specimens (2 controls and 3 embolized) were later treated with decreasing concentrations of ethanol before they were fixed in formalin for histologic examination.

Results

The first celiac angiography was successfully performed in 16 rats (4 rats in the control group and 12 rats in the embolization group) and revealed tumors in 13 (2 rats in the control group and 11 rats in the embolization group). The angiographic appearance was the same as described previously /12, 14/, with a hypovascular center surrounded by a hypervascular rim (Fig. 1). The hepatic artery was dilated, intrahepatic arteries displaced, and tortuous tumor vessels supplied the tumor (Fig. 2). Sometimes, vascular lakes could be seen within the tumor (Fig. 2).

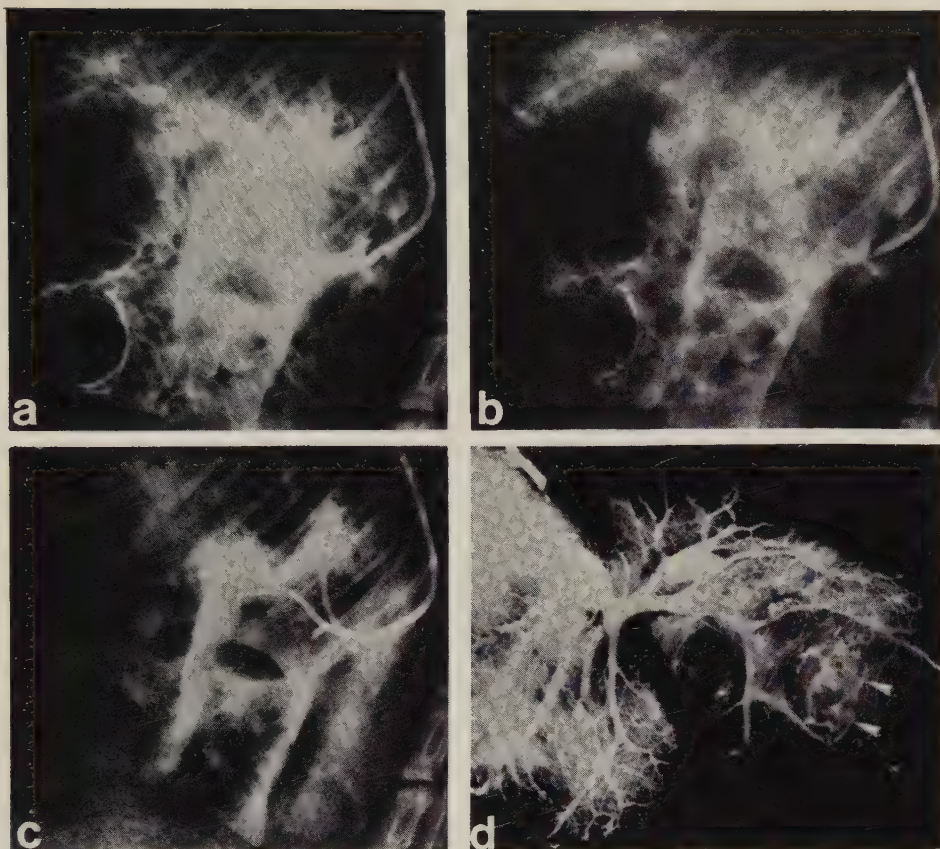


Fig. 1. Animal 16. Celiac angiography, lateral projection (catheter from carotid artery). A/ Arterial phase showing a hypovascular tumor displacing branches of the hepatic artery. B/ A hypervascular rim surrounding the tumor is seen in the capillary phase. C/ After ethanol embolization the hepatic artery is totally occluded at the periphery. No arterial circulation to the tumor can be seen. D/ Vascular lakes (arrow heads) filled with Microfil via the portal vein injection can be seen on radiogram of the liver specimen.

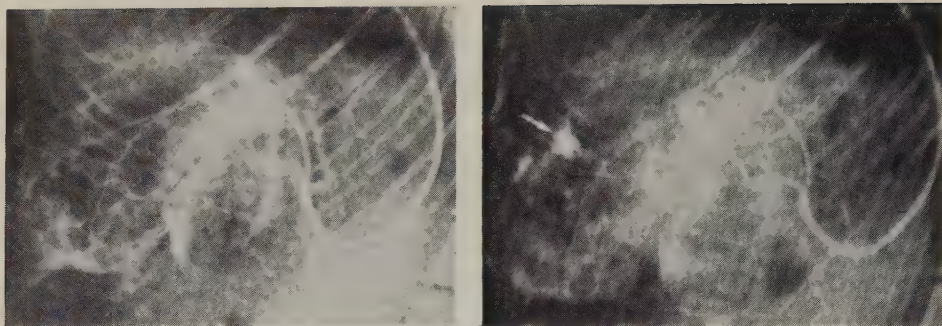


Fig. 2. Animal 15. Celiac angiography, lateral projection (catheter from carotid artery). A/ The tumor receives its blood from tortuous tumor vessels. B/ After ethanol embolization some tumor vessels are occluded. Vascular lakes (arrow) within the tumor.

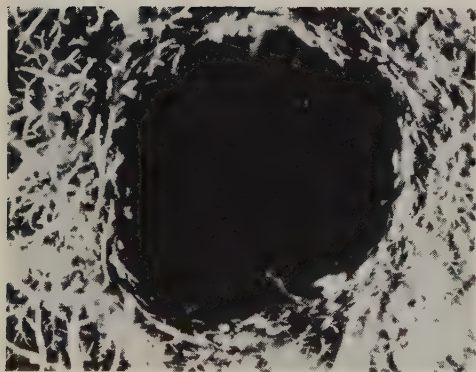


Fig. 3. Animal 4. Control. Microfil injected via the portal vein. The tumor appears as an avascular area. Small branches of the portal vein end at the margins of the tumor.

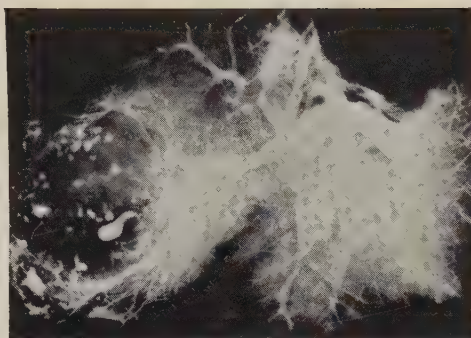
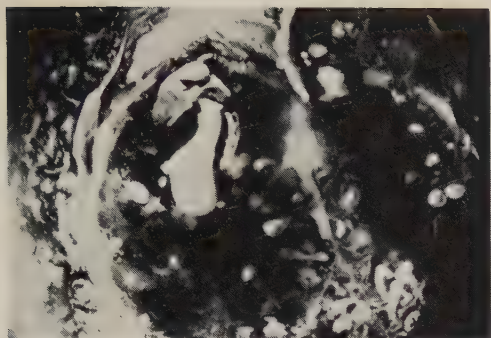


Fig. 4. Animal 18. A/ Four hours after ethanol embolization, Microfil was first injected into the portal vein and subsequently into the hepatic artery. Tumor lakes were filled with yellow color Microfil (portal vein). No orange Microfil inside the tumor lakes. B/ Radiogram of the liver specimen showed many tumor lakes filled from the portal vein. Vascular pattern of Microfil preparation in good agreement with the findings on the radiogram.

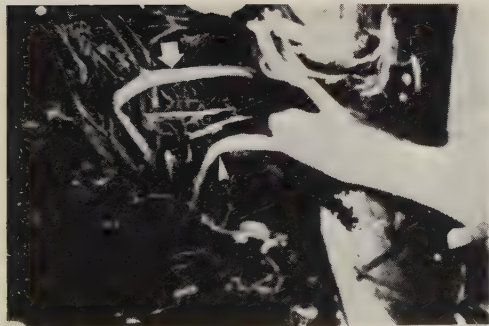


Fig. 5. Liver metastasis from colon carcinoma in man. White color Microfil was first injected into the portal vein and then orange Microfil into the hepatic artery. A branch of the hepatic artery (arrow) in company with a branch of the portal vein (arrow head) participate in the formation of a plexus of tumor vessels.

In order to evaluate the effect of embolization a second angiography was performed in 10 rats. Peripheral occlusion of the hepatic artery was obtained in 6 rats and proximal occlusion in 4 rats (Figs. 1 c, 2 b).

In the control group 4 rats were killed one hour to 5 days after angiography and another 4 rats were killed 2 weeks after inoculation without preceding angiography. In the embolization group, rats were sacrificed or died one hour to 3 days following embolization. The livers were perfused with Microfil in all 20 rats and the results are shown in Table 1. In the control group, the portal vein was exclusively injected in 4 rats (Nos. 1 - 4) and no tumor lakes were filled by Microfil. The tumor appeared as an avascular area and the branches of the portal vein abruptly ended at the edge of the tumor (Fig. 3). When the hepatic artery (3 rats) or both vessels (one rat) were injected in the remaining 4 rats (Nos. 5 - 8), filling of tumor lakes was obtained, and in one rat (No. 8) exclusively from the portal vein.

In the gelfoam group filling of tumor lakes from the portal vein was observed in 2 rats (cases 9 and 12).

In the ethanol group, filling of tumor lakes by the portal vein was seen in all rats except one (No. 15) (Fig. 4). Sometimes, connections between the tumor lakes and peripheral sinusoids were identified.

Correlation between the Microfil vascular preparations and radiograms of specimens was made in all 20 rats. The vascular architecture of the tumors as seen radiographically corresponded well to the appearance of the Microfil preparations (Fig. 4).

Discussion

It is evident from experimental studies /6, 15, 16/ that the blood supply of small liver tumors is derived from both the hepatic artery and the portal vein. The question still remains, however, how important the portal vein is in the nourishment of these tumors. From Microfil studies in the experimental animal /13/, as well as in man /17/, it has been demonstrated that tumors are perfused via peripheral sinusoids or small, newly formed vessels from surrounding sinusoids. When human liver specimens were studied, the branches of the portal vein participated directly in the formation of the peripheral plexus of tumor vessels (Fig. 5). As experimental studies have shown that the periphery of the tumor plays an important role for its development, the significance of the portal vein in the nourishment of the tumor should not be underestimated /7, 16/. Furthermore, portal vein ligation has been tried in patients with unresectable carcinoma of the liver and significant palliation attained in some patients /18/.

In the present study, tumor lakes could be filled by either the hepatic artery or the portal vein injection. The pathologic basis of the tumor lake is not well understood and it has been ascribed to areas of necrosis or vascular degeneration /4/. Histological examinations have shown that tumor lakes are in fact dilated abnormal vessels /17, 19/.

Previous studies /20, 21/ have shown that there are several arterio-portal communications within the liver, e.g. 1/ the peribiliary arterial plexus, 2/ the

vasa vasorum of the portal vein, and 3/ direct arterio-portal connections in the sinusoids. The presence of these arterio-portal communications may explain the fact that the frequency of tumor lakes filled from the portal vein in the embolization group was much higher than that in the control group. Because the hepatic artery and its peripheral branches are occluded after embolization, the portal vein takes over and the tumor receives its blood supply from the portal vein.

In the embolization groups, as opposed to the control group, the fact that the tumor lakes could be perfused by the portal vein injection in altogether 8 rats shortly following arterial embolization was a significant observation. This might be of importance for the planning of future improved treatment of hepatic neoplasms. Based upon the findings reported previously /6, 7, 15, 16, 18/ as well as here, there is reason to believe that peripheral embolization of the hepatic artery combined with intraportally delivered chemotherapeutic agents may be more effective than dearterialization alone in the treatment of liver tumors. However, in order to verify the accuracy of this suggestion, further documentation from clinical case experiences is required.

REFERENCES

1. BREEDIS C. and YOUNG G.: Blood supply of neoplasms in the liver. *Amer J Pathol* 30 (1954), 969 - 985
2. HEALY J.E.: Vascular patterns in human metastatic liver tumors. *Surgery* 120 (1965), 1187 - 1193
3. ROGERS W., EDLICH R.F., LEVIS D.V. and AUST J.B.: Tumor blood flow. I. Blood flow in transplantable tumors during growth. *Surg Clin North Amer* 47 (1967), 1473 - 1482
4. ACKERMAN N.B. and HECHMER P.A.: The blood supply of experimental liver metastases. V. Increased tumor perfusion with epinephrine. *Amer J Surg* 140 (1980), 625 - 631
5. SOO C-S., CHUANG V.P., WALLACE S., CHARNSANGAVEJ C. and CARRASCO H.: Treatment of hepatic neoplasm through extrahepatic collaterals. *Radiology* 147 (1983), 45 - 49
6. ACKERMAN N.B., LIEN W.M., KONDI E.S. and SILVERMAN N.A.: The blood supply of experimental liver metastases. I. The distribution of hepatic artery and portal vein blood to "small" and "large" tumor. *Surgery* 66 (1969), 1067 - 1072
7. HONJO I. and MATSUMARA H.: Vascular distribution of hepatic tumors. Experimental study. *Rev Int Hepat* 15 (1965), 681 - 690
8. LIEN W.M. and ACKERMAN N.B.: The blood supply of experimental liver metastases. II. A microcirculatory study of the normal and tumor vessels of the liver with the use of perfused silicone rubber. *Surgery* 68 (1970), 334 - 340
9. STEELE Jr G. and SJÖGREN H-O.: Cross-reacting tumor associated antigen(s) among chemically induced rat colon carcinomas. *Cancer Res* 34 (1974), 1801 - 1807
10. EKELUND L. and OLIN T.: Catheterization of arteries in rats. *Invest Radiol* 5 (1970), 69 - 74
11. EKELUND L., HENRIKSON H., OLIN T. and SJÖGREN H-O.: Angiography in hepatic cysts and tumors in the rat. *Invest Radiol* 9 (1974), 396 - 403
12. EKELUND L., STIGSSON L., JONSSON N. and SJÖGREN H-O.: Transcatheter arterial embolization of normal liver and experimental hepatic tumors in rats. *Acta Radiol Diagnosis* 18 (1977), 641 - 651
13. ACKERMAN N.B.: The blood supply of experimental liver metastases. IV. Changes in vascularity with increasing tumor growth. *Surgery* 75 (1974), 589 - 596
14. STIGSSON L., EKELUND L., JONSSON N. and SJÖGREN H-O.: Transcatheter arterial embolization of experimental hepatic tumors in the rat. *Acta Radiol Diagnosis* 20 (1979), 422 - 432

15. ACKERMAN N.B.: Experimental studies on the circulatory dynamics of intrahepatic tumor blood supply. *Cancer* 29 (1972), 435 - 439
16. NILSSON L.A.V. and ZETTERGREN L.: Effect of hepatic artery ligation on induced primary liver carcinoma in rats. Preliminary report. *Acta Pathol Microbiol Scand* 71 (1967), 187 - 193
17. LIN G., LUNDERQUIST A., HÄGERSTRAND I. and BOIJSEN E.: Post-mortem examination of the blood supply and vascular pattern of small liver metastases in man. *Surgery*. In press
18. HONJO I., SUZUKI T., OZAWA K., TAKASAN H., KITAMURA O. and ISHIKAWA T.: Ligation of a branch of the portal vein for carcinoma of the liver. *Amer J Surg* 130 (1975), 296 - 302
19. EKELUND L., JONSSON N. and LUNDERQUIST A.: Tumor vessels. Angiographic-histopathologic correlation. *Radiologe* 17 (1977), 95 - 102
20. CHO K.J. and LUNDERQUIST A.: Experimental hepatic artery embolization with gelfoam powder. *Invest Radiol* 18 (1983), 189 - 193
21. BOOKSTEIN J.J., CHO K.J., DAVIS G.B. and DAIL D.: Arterioportal communications. Observations and hypotheses concerning transsinusoidal and transvasal types. *Radiology* 142 (1982), 581 - 590

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MICROVASCULATURE ARCHITECTURE OF
SMALL LIVER METASTASES IN MAN
A correlation between Microfil preparations
and histologic sections

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Investigated Radiology: Received October 31, 1983, and accepted for
publication, after revision, January 4, 1984

Abstract

The hepatic artery and the portal vein of 12 human cadaver livers with metastases of various sizes and origins were injected with Microfil. The microvascular appearances of the metastases were studied in order to receive an explanation to findings at angiography and contrast enhanced computed tomography. Histologic examinations were also performed of Microfil-injected specimens.

Key words

Liver - Liver metastases - Hepatic artery - Portal vein

Microfil perfusion technique has been widely used in the study of the microvascular patterns of various organs /1 - 5/. In the present study the technique was used on human cadaver livers in order to find a correlation between the Microfil preparations and findings at angiography and computed tomography as well as histologic sections of hepatic tumours.

Material and methods

Twelve human livers with metastases of various sizes and origins were examined at autopsy. The primary sites included carcinoma of breast (3), lung (2), colon (one), prostate (2), pancreas (one), gallbladder (one), and in addition malignant lymphomas (2). There were 8 men and 4 women, whose ages ranged from 35 to 86 years.

The technique for the liver perfusion has been described previously /5/. The portal vein and the hepatic artery were catheterized and injected with Microfil (Canton Bio-Medical Products, Inc., Boulder, CO) by hand. Injection pressure was not recorded, but the degree of vascular filling was interpreted from vessels visualized on the liver surface. White or yellow Microfil (MV-112 or MV-122) was usually first injected into the portal vein (9 cases), then orange Microfil (MV-117) was injected into the hepatic artery. In 2 cases the hepatic artery was first injected and in one case the hepatic artery and the portal vein were injected simultaneously. If both vessels were perfused subsequently in the same liver lobe, additional curing agent was added to the first injected material to avoid mixture of two colors. The second injection was performed 2 to 3 hours later. To reduce the volume of Microfil needed, the portal branch of only one lobe of the liver was injected; the other was ligated after the catheter was inserted into the main stem of the portal vein. Thirty to 40 ml of Microfil was needed for the hepatic artery and 40 to 50 ml for the portal vein. After completed injections, the specimens were kept in a refrigerator overnight.

The liver pieces containing metastatic nodules surrounded by normal parenchyma were cleared by dehydration in increasing concentrations of ethanol. Finally, the specimens were placed in methylsalicylate. When the specimens be-

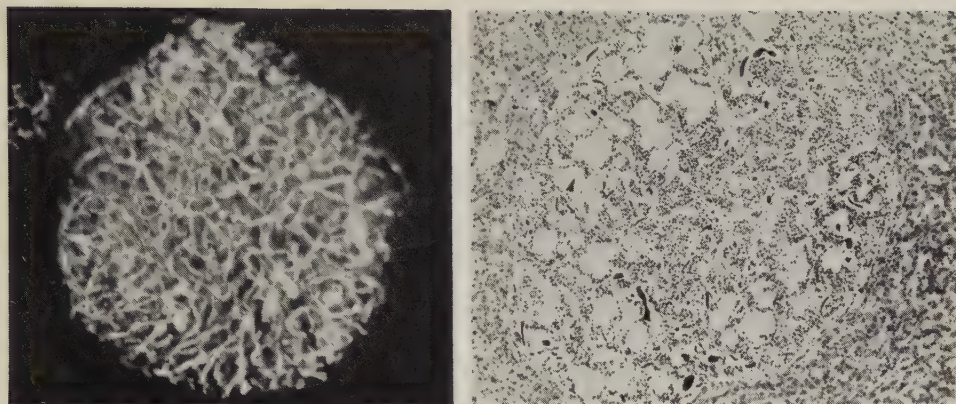


Fig. 1. 1.5-mm metastasis from breast carcinoma. A/ Microfil preparation. Richly vascularized metastatic nodule appeared as a vascular sphere. Mostly normal tapering vessels, but irregular and wider vessels appeared in the peripheral part of the tumor. B/ Histologic section corresponds well to A. Some tumor vessels were very thin, while others were dilated in the peripheral parts of the tumor (x 56).

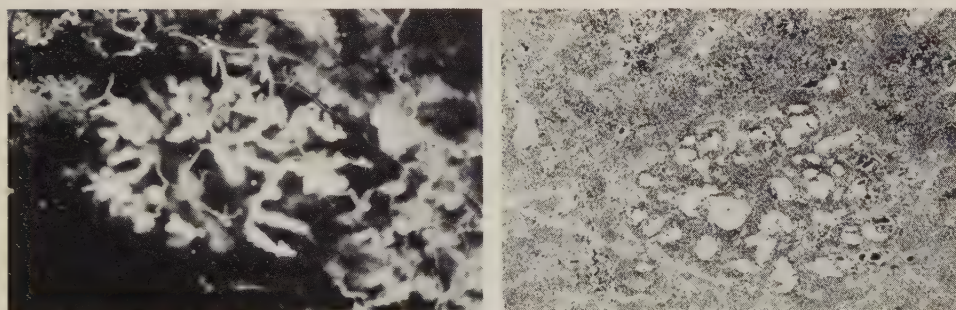


Fig. 2. Poorly vascularized metastasis from prostatic carcinoma. A/ Vascular lakes are mostly filled with white-colored Microfil from the portal vein, but some vascular lakes (gray) are filled with two colors of Microfil (both from the hepatic artery and the portal vein). B/ Histologic examination demonstrates many dilated vessels in the tumor (x 20).

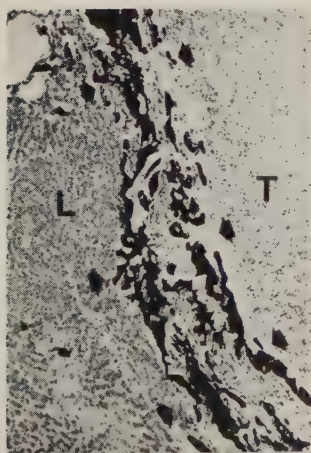


Fig. 3. Liver metastasis from gallbladder carcinoma. T = tumor, L = liver tissue. Histologic sections show the congested sinusoids (arrows) filled with Microfil (black) surrounding the tumor (x 85).

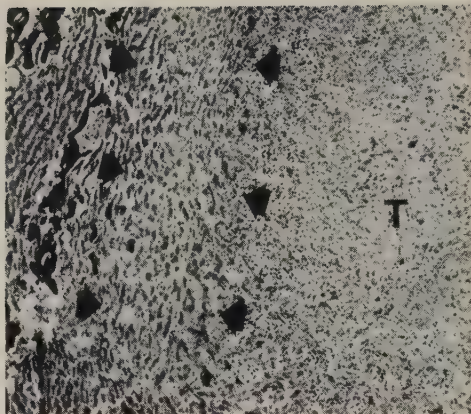
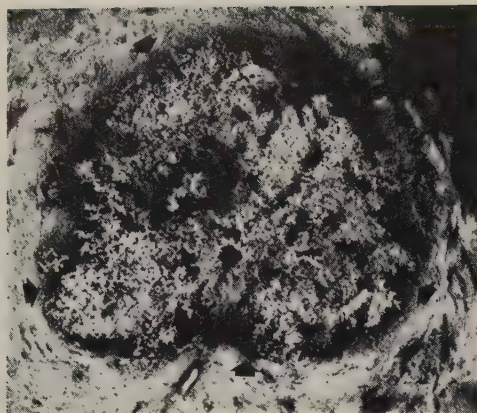


Fig. 4. Liver metastasis from prostatic carcinoma. A/ Microfil preparation. Tumor vessels as well as normal sinusoids filled from portal vein (white). An avascular zone (black) surrounding periphery of the tumor (arrows). B/ T = tumor. A zone of closely lying liver plates (arrows) with compressed liver sinusoids corresponds to the avascular zone peripheral to the tumor in A. (x 60).

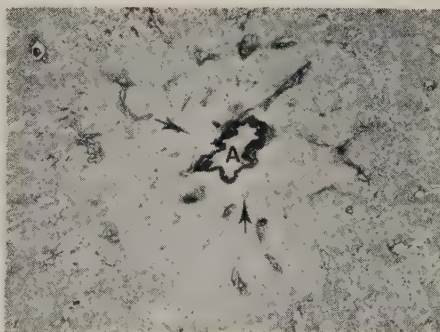
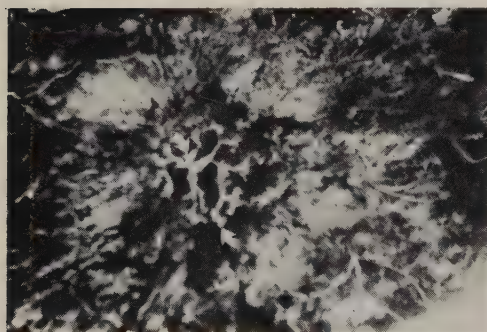


Fig. 5. 6-mm metastasis from lung carcinoma. A/ Microfil preparation. Several vascular lakes (arrows) are seen in central part of the tumor. B/ Histologic section demonstrates a thrombosed artery (A) in the center of the tumor surrounded by the vascular lakes (arrows). (x 14).



Fig. 6. 1.5-mm metastasis from breast carcinoma. Tumor vessels are directly filled from branches of the hepatic artery (arrows). A small branch of the portal vein (open arrow) shows a connection (arrow head) to the hepatic artery.

came transparent, they were examined under the stereomicroscope. They were then treated with decreasing concentrations of ethanol, embedded in paraffin, sectioned and stained with hematoxyline-erythrosin, and sometimes with reticulin and/or collagen stains for histology.

Twenty-three liver metastases from the 12 cadavers were examined.

Results

The size of the metastatic nodules was between 1 and 20 mm, most nodules were 5 to 10 mm. Among the 23 specimens, 8 were very rich in vessels, 5 contained a moderate amount of vessels, and 10 were rather avascular.

Tumor vessels and so-called tumor lakes. In the 8 highly vascularized nodules, the tumor appeared as a vascular sphere, which corresponded well to the appearance of the histologic section (Fig. 1 A and B). Some tumor vessels were thin and tortuous, while others were irregular with dilatations and narrowings (Fig. 1 B). The diameter of the vessels was usually smaller in highly vascularized nodules than in the poorly vascularized ones. In the latter, dilated abnormal vessels lined by a single layer of endothelial cells were found. Such vascular lakes could be filled by injections from the portal vein as well as from the hepatic artery (Fig. 2 A and B).

Periphery of tumor. Two types of vascular patterns in the Microfil preparations could be seen in the periphery of the tumor nodule. Sinusoids peripheral to the tumor nodules appeared dilated (Figs. 1 and 3) or an avascular zone surrounded the periphery of the tumor (Fig. 4 A). When the sinusoids were dilated, the liver plates were found thin and atrophic in histologic sections. The avascular zone corresponded in histologic sections to several plates of liver cells lying closely together with compressed sinusoids (Fig. 4 B). In some sections avascular peripheral regions corresponded to portal veins occluded by tumor thrombi.

Center of tumor. Usually the central portion of a tumor had fewer vessels than its periphery. In metastases larger than 5 mm in diameter, an avascular zone could be seen in the center which usually corresponded to a necrotic area. The margins of the necrosis were irregular. In one specimen a thrombosed artery was seen in the center of the tumor (Fig. 5).

Connections between tumor vessels and vessels outside the tumor. Outside the tumor presinusoidal connections between the hepatic artery and the portal vein were frequently seen. When the hepatic artery was first injected, these connections could be demonstrated over the peribiliary arterial plexus and the vasa vasorum of the portal vein. Filling in the opposite direction of the hepatic artery from the portal vein was never seen when this vascular structure was first injected.

Tumor vessels could be directly connected with a small branch of the hepatic artery (Fig. 6) or with several small vessels surrounding sinusoids. Small branches of the hepatic artery in company with branches of the portal vein could participate in the formation of tumor vessels, which was also demonstrated on

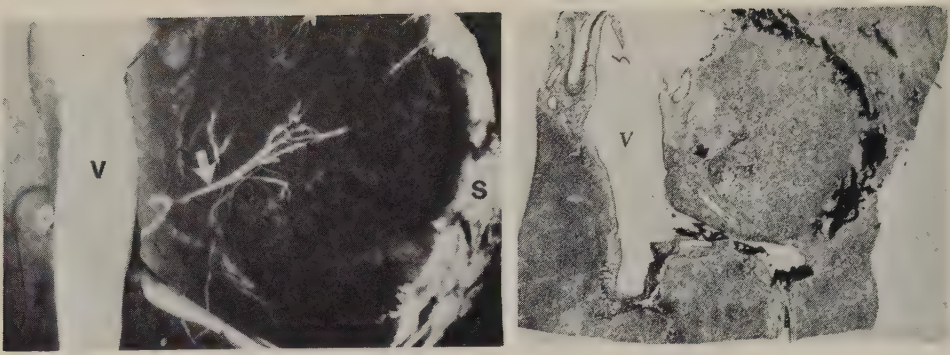


Fig. 7. Liver metastasis from breast carcinoma. A/ Microfil preparation. A tumor feeding vessel (arrow) directly arises from a portal branch (V) and extends into the tumor. Sinusoids (S) peripheral to the tumor are dilated and congested. B/ Histologic section corresponds well to A. The tumor feeding vessel (arrow) takes off from the portal branch (V). (x 8).

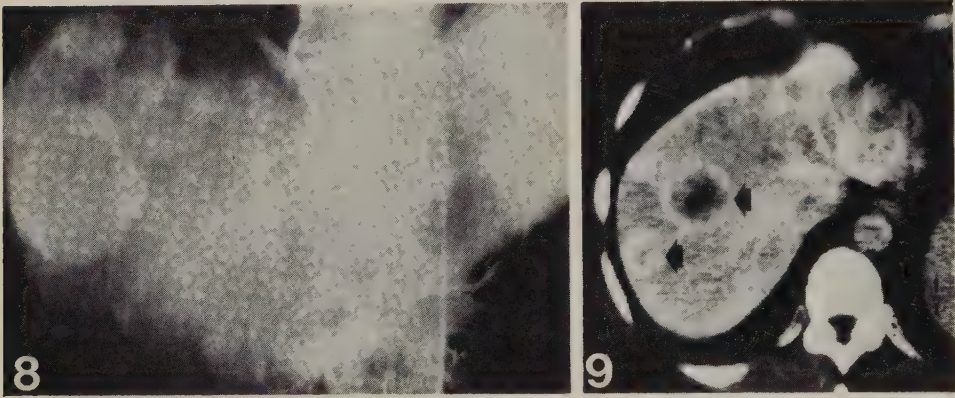


Fig. 8. Carcinoid metastases in the liver. Parenchymal phase of angiography shows multiple hypervascular metastases. Lesions with necrotic centers are surrounded by high-density rings.

Fig. 9. Liver metastases from colon carcinoma. CT enhanced by contrast injection into hepatic artery. Multiple metastatic nodules (arrows) appear as high-density rings with low-density centers.

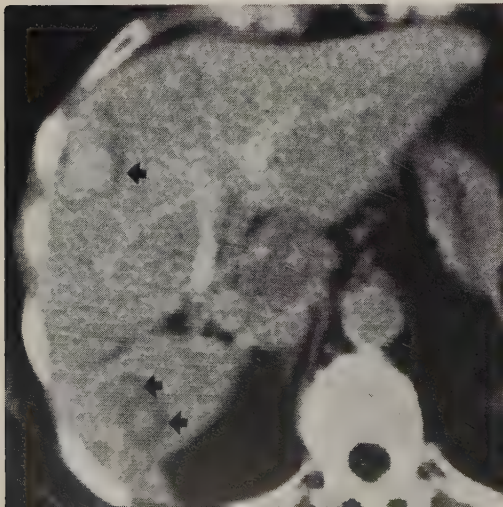


Fig. 10. Liver metastasis from colon carcinoma. CT enhanced by contrast injection into hepatic artery. Low-density rings in the periphery of tumor nodules (arrows).

histologic serial sections. Tumor vessels sometimes arose from a branch of the portal vein extending into the tumor nodule (Fig. 7). An investigation of the portal venous supply of the tumors is not the purpose of this article, and is discussed in detail elsewhere /5/.

Discussion

Highly vascularized hepatic tumors are usually well visualized on the angiograms (Fig. 8). REUTER and REDMAN considered the visualization due to contrast medium passing into the interstitial spaces of the tumor or into many small vascular channels inside the tumor /6/. From our study it has been shown that tumor vessels are often very thin, irregular, and tortuous. The flow of blood with contrast medium might be slowed down when it passes through these small vascular channels and the tumors become stained during a longer period of time than the normal liver parenchyma.

The histologic correspondence to the tumor lakes has not been well understood. It has been suggested they represent areas of necrosis connected with a tumor vessel or vascular degeneration /6, 7/. In cavernous hemangioma, tumor lakes were proved to be large venous spaces lined by a single layer of endothelial cells /8/. According to correlations between Microfil vascular preparations and the histologic sections, tumor lakes are dilated abnormal vessels lined by a single layer of endothelial cells (Fig. 2 B). So far, we have not had the opportunity to study cavernous hemangioma with the same technique.

At angiography or contrast enhanced computed tomography a high- or low-density ring (Figs. 9 and 10) can be seen in the periphery of the tumor, the former more common than the latter /9 - 11/. This study suggests that the peripheral high-density ring can have two explanations: 1) congested, dilated sinusoids outside an hypovascular tumor (Fig. 3); and 2) hypervascular tumor with a necrotic center (Fig. 8). Thus, the hypervascularity in the periphery of the tumor must not necessarily mean tumor vessels. Avascularity in the center of the tumor demonstrated on Microfil preparations corresponded in most cases to necrosis on histology. However, in a few cases avascularity was a technical artifact and central tumor necrosis was not noted histologically /5/.

A low-density ring around a tumor is histologically explained by several layers of liver cells with compressed, empty sinusoids (Fig. 4), or fatty degeneration of liver cells /11/. When CT examinations are performed, this ring is demonstrated after contrast enhancement (Fig. 10), but is sometimes too thin to be seen.

REFERENCES

1. HASE T.: Observation on the microcirculatory architecture of the rat liver. *Anat Rec* 156 (1966), 157
2. REYNOLDS D.G.: Silicone rubber technique for microvascular study. *Lab Mgmt* 6 (1968), 24
3. CHO K.J. and LUNDERQUIST A.: The peribiliary vascular plexus: The microvascular architecture of the bile duct in the rabbit and clinical cases. *Radiology* 147 (1983), 357
4. DAVIDSON J.W. and HOBBS B.B.: The lymphatic microcirculatory spaces in lymph nodes during an immune response. *Invest Radiol* 9 (1974), 82
5. LIN G., LUNDERQUIST A., HÄGERSTRAND I. and BOIJSEN E.: Post-mortem examination of the blood supply and vascular pattern of small liver metastases in man. *Surgery* (Acc for publ)
6. REUTER S.R. and REDMAN H.C.: *Gastrointestinal angiography*. 2nd ed. Philadelphia: W B Saunders (1977)
7. ACKERMAN N.B. and HECHMER P.A.: The blood supply of experimental liver metastases. V. Increased tumor perfusion with epinephrine. *Amer J Surg* 140 (1980), 625
8. MOSS A.A., CLARK R.E. and PALUBINSKAS A.J.: Angiographic appearance of benign and malignant hepatic tumors in infants and children. *Amer J Roentgenol* 113 (1971), 61
9. WOOTEN W.B., BERNARDINO M.E. and GOLDSTEIN H.M.: Computed tomography of necrotic hepatic metastases. *Amer J Roentgenol* 131 (1978) 839
10. MARCHAL G.L., BAERT A.L. and WILMS G.E.: CT of noncystic liver lesions. Bolus enhancement. *Amer J Roentgenol* 135 (1980), 57
11. ANGRES G., CARTER J.B. and VELASCO J.M.: Unusual ring in liver cell adenoma. *Amer J Roentgenol* 135 (1980), 172

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LOW DENSITY RING IN LIVER METASTASES ON CT

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Short title: Low density ring...

Abstract

A case with liver metastases from colon carcinoma showing a low density ring sign is presented. Cadaver studies suggest that this sign can be produced by compressed liver cells and sinusoids.

Key terms

Liver - Liver metastases - Low density ring - Computed tomography

With few exceptions intravenous or intraarterial administration of contrast markedly improves visualization of focal lesions within the liver when computerized tomography (CT) is performed. In most cases, the attenuation of the normal liver parenchyma increases more than that of a focal lesion. However, in rare cases, hypodense lesions on a pre-contrast study can turn isodense /1/, and isodense lesions can remain isodense after contrast administration /2/.

Contrast enhancement often shows a high density ring in the periphery of a tumor or peripheral to a tumor corresponding to tumor vascularity or congestion of sinusoids, respectively /3/. A low density peripheral ring around the tumor has also been described /4/ produced by hepatocytes with large fat vacuoles and was suggested to be specific for liver cell adenoma.

Recently we examined a patient with liver metastasis from colon carcinoma showing the same hypodense ring around the tumor deposits.

A study of tumor vascularity on cadaver livers combined with histologic examinations have given a second explanation to this phenomenon.

Case report

A 61-year-old male was operated upon because of carcinoma of the sigmoid, with left hemicolectomy. During operation several metastases were found in both liver lobes. Two months later angiography CT demonstrated multiple lesions in both liver lobes. On plain scans the lesions consisted of a low density area measuring 32 HU (Hounsfield units), some of which with a somewhat denser center, compared to 54 HU in normal liver tissue (Fig. 1 A).

After intravenous contrast enhancement the lesions measured 53 HU compared to 73 HU for liver tissue (Fig. 1 B) and after intraarterial contrast enhancement via the celiac axis the lesions measured 101 HU, the same as normal liver parenchyma. Around the lesions low density rings were clearly demonstrated (Fig. 1 C) but the limited thickness of these rings did not allow measurement of the HU without partial volume effect.

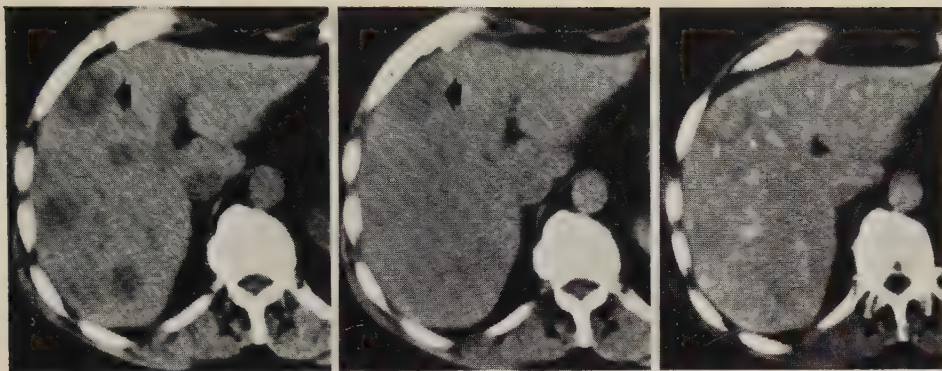


Fig. 1. Patient with liver metastases from colon carcinoma: A/ Unenhanced CT examination shows multiple hypodense lesions in the right liver lobe, one of which with a central higher density (arrow). B/ The same CT slice after intravenous contrast enhancement. The lesion still appears hypodense but almost uniform (arrow). Other lesions have changed almost to isodensity compared to the surrounding liver parenchyma. C/ After intraarterial contrast enhancement (via a catheter in the celiac axis) the lesion turns isodense to liver parenchyma but is surrounded by a low density ring (arrow heads). Other lesions are only faintly visible.

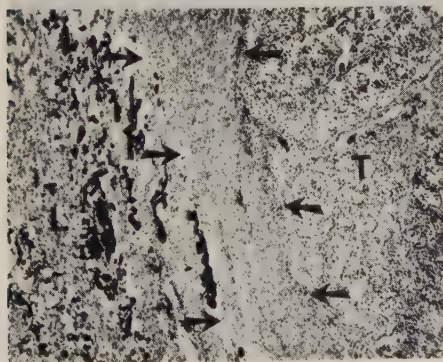
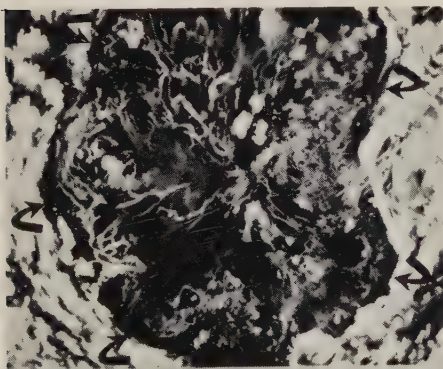


Fig. 2. Liver metastatic nodule from colon carcinoma. A/ Microfil was injected via both the portal vein and the hepatic artery. Tumor vessels as well as normal sinusoids were filled with Microfil. An avascular zone surrounds the periphery of the metastatic nodule (curved arrows). B/ Histologic section of the metastatic nodule. T = tumor, L = liver tissue. A zone of compressed liver sinusoids with liver plates lying close together (arrows). HE x 67. Appears as an avascular peripheral ring in the Microfil preparation.

Cadaver examinations

Fifteen cadaver livers with metastases of various origin were examined. The hepatic artery and the portal vein were injected with silicone rubber compounds (Microfil, Canton Bio-Medical Products Inc., Boulder, Colorado, USA) of different colors. After a clearing procedure /5/ the tumors were examined under a dissecting microscope, photographed, and finally examined histologically.

In four cases an avascular zone around the tumor deposits was found (Fig. 2 A). Histologically, this hypovascular zone corresponded to plates of liver cells packed tightly together with compressed sinusoids (Fig. 2 B).

Discussion

Liver tumors often appear with a densely stained periphery in the parenchymal phase of an angiographic examination /5, 7, 8/ as well as on contrast enhanced CT. At angiography, a lucent ring around the tumor has been demonstrated in focal nodular hyperplasia /9/, and at CT a low density ring has been seen around a hepatic adenoma and suggested to be specific for this entity /4/. We have seen this low density ring also at CT performed on a patient with metastases from colon carcinoma.

The appearance of the metastatic lesion on CT as compared to that of normal liver parenchyma is of great interest because of its variations before and after administration of contrast medium. On pre-contrast examination the lesions were hypodense, one of them with a central small denser area. After intravenous contrast enhancement the lesion was still hypodense but now uniform. The greatest enhancement of the lesions was seen after administration of intraarterial contrast medium making them isodense compared to normal liver parenchyma. This can be explained by simultaneous contribution of contrast medium from the hepatic artery and the portal vein.

The peripheral change in vascularization was here best demonstrated after i.a. administration of contrast. A low density ring demonstrated around the tumors was found to be produced by compressed liver cells and sinusoids. Cadaver studies supported this hypothesis.

REFERENCES

1. FOLEY W.P., BERLAND L.L., LAWSON T.L., SMITH D.F. and THORSEN M.K.: Contrast enhancement technique for dynamic hepatic computed tomographic scanning. *Radiology* 147 (1983), 797 - 803
2. SAKO M., LUNDERQUIST A., OWMAN T., MÅRTENSSON H. and NOBIN A.: Angiographic and computed tomographic appearance of secondary carcinoid of the liver. *Cardiovasc Intervent Radiol* 5 (1982), 90 - 96
3. LIN G., LUNDERQUIST A., HÄGERSTRAND I. and BOIJSSEN E.: Post-mortem examination of the blood supply and vascular pattern of small liver metastases in man. *Acc for publ in Surgery*
4. ANGRES G., CARTER J.B. and VELASCO J.M.: Unusual ring in liver cell adenoma. *Amer J Roentgenol* 135 (1980), 172 - 179
5. CHO K.J. and LUNDERQUIST A.: Experimental hepatic artery embolization with Gelfoam^R powder. Microfil^R perfusion study of the rabbit liver. *Invest Radiol* 18 (1983), 189 - 193
6. WOOTEN W.B., BERNARDINO M.E. and GOLDSTEIN H.M.: Computed tomography of necrotic hepatic metastases. *Amer J Roentgenol* 131 (1978), 839 - 842
7. MARCHAL G.L., BAERT A.L. and WILMS G.E.: CT of noncystic liver lesions: Bolus enhancement. *Amer J Roentgenol* 135 (1980), 57 - 65
8. ITAI Y., FUYUI S., ARAKI T., YASHIYO N. and TASAKA A.: Computed tomography of cavernous hemangioma of the liver. *Radiology* 137 (1980), 149 - 155
9. REUTER S.R. and REDMAN H.C.: *Gastrointestinal angiography*. W.B. Saunders, Philadelphia (1977), p. 139

SELECTIVE ANGIOGRAPHY IN DIAGNOSING PRIMARY HEPATIC CARCINOMA

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Selective and superselective hepatic arteriography is valuable in diagnosing primary hepatic carcinoma. Tumor vessels, tumor stain, vessel stretching displacement, vascular encasement, arteriovenous shunt, pool or lake-like collection of contrast medium and tumor emboli formation occurring during arterial phase and irregular mottling during parenchymal phase are characteristic manifestations. Among them, tumor vessels and tumor stain are the 2 pathognomonic signs. After evaluating the correlation of the arteriographic features, isotope scan, clinical data and pathologic findings, it is obvious that arteriography is superior to isotope scan in establishing a correct diagnosis. It can facilitate treatment when the catheter is retained for drip chemotherapy.

Selective arteriography (SA) or superselective arteriography has been widely used in diagnosing abdominal diseases of the solid organs and is particularly valuable in diagnosing hepatic tumors. SA studies in 98 cases of primary hepatic carcinoma and the results are presented.

CLINICAL DATA

Performed in 98 cases clinically diagnosed or suspected of having hepatic carcinoma, SA was successful in 94 and failed in 4. Of the 94 cases 87 were male and 7 female. Their

age ranged from 18-67 years and 64 cases (67%) were above 40.

Celiac SA was done in 79 and superselective common hepatic arteriography in 7. In 4, superselective common hepatic arteriography was performed following celiac SA and in another 4 superior mesenteric SA was done following celiac SA. The results of these contrast examinations include 82 positive and 12 negative. The relationships between AFP, isotope scans and arteriograms of 88 cases are listed in Table 1. 38 of 92 positive cases were operated upon. They were all confirmed as hepatic cell carcinoma pathologically. The remaining 44 were also confirmed by clinical data. Of 12 negative cases, 4 were operated upon and 3 were false negative, carcinoma being found. The other 8 negative cases were carefully studied and followed with hepatic carcinoma excluded clinically.

Among 42 surgically confirmed cases, 9 had positive AFP but negative isotope scans. The tumor masses were all within 5 cm in diameter, the smallest being only 1.5 cm.

ARTERIOGRAPHIC TECHNIC

After puncturing the femoral artery percutaneously by Seldinger's method, a special angled No. 7 end hole catheter is often inserted into the femoral artery. Under TV monitor, the catheter is passed into the abdominal aorta up to the level of T₁₂ or L₁ (a metal mark being placed on the com-

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Table 1. Correlation of AFP and isotope scans (IS) and arteriography in 88 cases

Examination	Arteriography	
	Positive (cases)	Negative (cases)
AFP(+) IS(+)	41	1
AFP(+) IS(-)	24	4
AFP(-) IS(+)	10	
AFP(+) ?IS(-)		3
AFP(-) IS(+)?		1
AFP(-) IS(-)	1	3
Total	76	12

Table 2. Arteriographic signs of primary hepatic cancer in 82 cases

Signs	Cases	%
Tumor vessel	65	79.27
Tumor stain	68	82.93
Vascular stretching, displacement and distortion	46	56.10
Vascular encasement	38	46.34
Intrahepatic filling defects and irregular mottlings	13	15.85
Arterio-venous shunt	24	29.27
Lake-like	44	53.66
Portal vein thrombosis	17	20.73

parative part of the patient's back). By turning the catheter tip anteriorly and then moving it up and down, it can be slipped into the celiac artery. If the superior mesenteric artery is selected, the same manoeuvre should be performed at L₁ level.

In order to make sure that the tip of catheter is within the selected vessel, 5-6 ml contrast medium is injected manually. For superselective hepatic arteriography, the tip of catheter should be pushed further upward and to the right.

40-60 ml 76% urografin is used for celiac or superior mesenteric SA and 30-40 ml for common hepatic SA. A Gidlund high pressure injector is used at 3-4 kg/cm² pressure

for celiac SA or superior mesenteric SA and 2 kg/cm² for common hepatic SA. Serial films are taken at one film per second for 5 seconds and one film every 2 seconds thereafter up to 20 seconds.

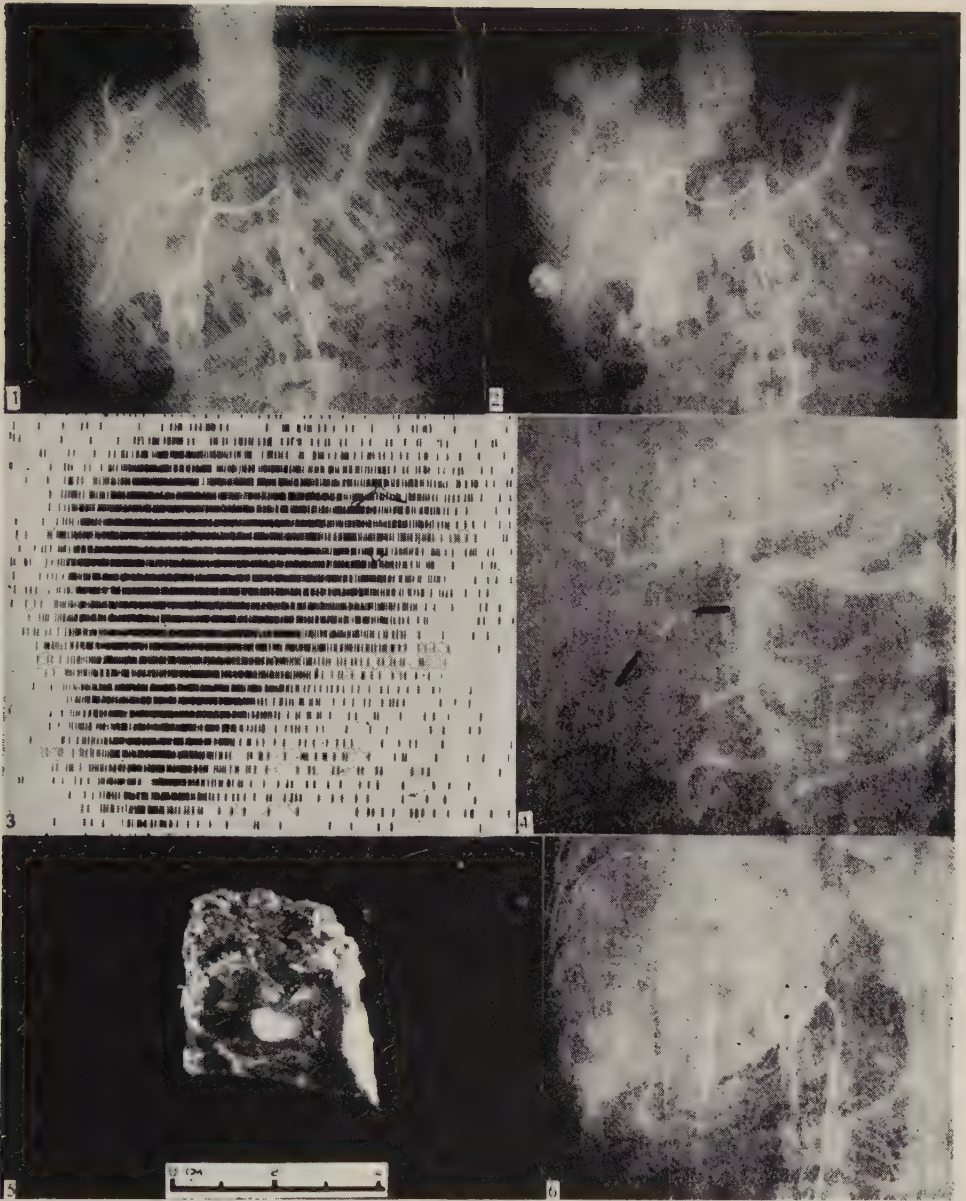
ARTERIOGRAPHIC MANIFESTATIONS

SA arterial, capillary and venous phase manifestations vary in primary hepatic carcinoma, the major arteriographic signs are listed in Table 2.

Tumor vessels. In 65 cases these appear disorderly in distribution with uneven lumens at the tumor site and spherical shape fistling ball sign. Frequently the feeding vessels are dilated and distorted (Figs 1-3). Because primary hepatic carcinoma is usually hypervascular, tumor vessels are often visualized, being present in 93% of our series. This sign is pathognomonic for primary hepatic carcinoma and tumors as small as 1-2 cm in diameter may be diagnosed. In contrast, metastatic carcinomas are usually hypovascular and tumor vessels are rarely seen.^{1,2}

Tumor stain. In 68 cases this sign appears during the capillary phase. Tumor stain with contrast medium has higher density than the surrounding hepatic parenchyma so tumor size and contour are clearly depicted (Fig 2). Small hepatic carcinomas opacify distinctly as solitary spherical lesions, whereas the larger ones are slightly lobulated. This sign is clearly shown in our series of superselective hepatic arteriograms (Figs 4,5).

More cases with abundant tumor vessels in the arterial phase usually show tumor stains in the capillary phase. Rarely does tumor stain appear clearly even if there are only a few tumor vessels in the arterial phase. For example, in 1 of our cases, only 2 dubious bushes of abnormal vessels were seen in the arterial phase, but 2 distinct small tumor stains were shown in the capillary phase so a definite diagnosis was made. In



Figs 1-3. Superselective common hepatic arteriography.

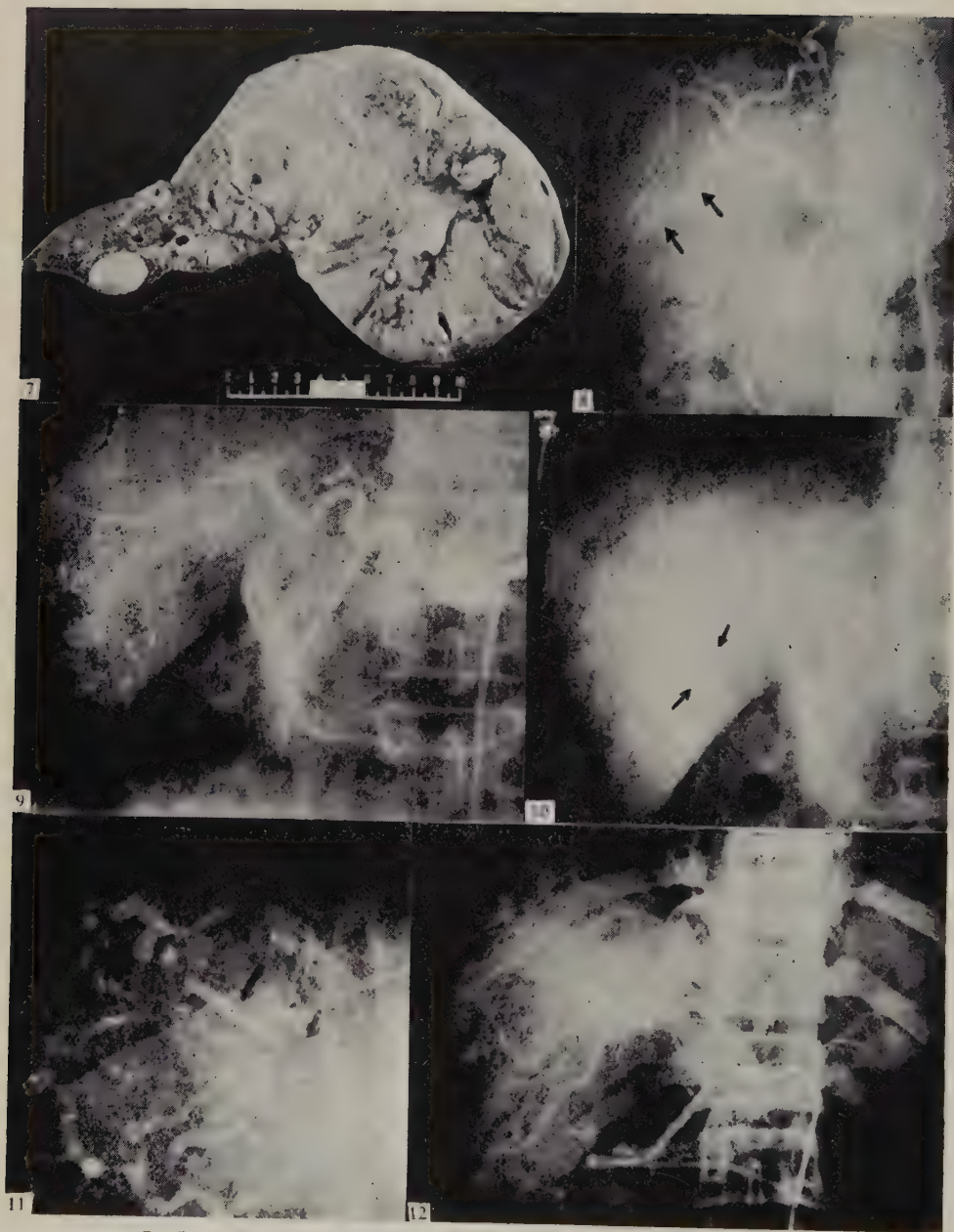
1. Numerous small tumor vessels are seen in the liver upper and lower portions. Feeding vessels are enlarged and distorted.
2. Capillary phase. Tumor stains appear. Densities are not homogeneous.
3. Isotope scan does not show space occupying lesion.

Figs 4, 5. Selective celiac arteriography.

4. A few abnormal vessels appear in the arterial phase (arrow).
5. Removed liver specimen, there is a small cancer 1.5 cm in diameter.

Figs 6, 7. Cadaveric hepatic arteriography.

6. The right hepatic artery and its branches are stretched, displaced and distorted around the tumor mass.



7. Liver specimen, huge hepatic carcinoma in the right liver lobe.

Fig 8. Superselective arteriography. The hepatic artery right lower branch is encased by carcinoma (arrow), no tumor vessels appear.

Figs 9, 10. Selective celiac arteriography.

9. Arterial phase: Numerous tumor vessels and tumor lake are seen in the lower portion of the right liver lobe.

10. Parenchymal phase: Homogeneous filling defects (arrow).

Fig 11. Selective celiac arteriography. The portal branches are opacified during the arterial phase (arrow).

Fig 12. Selective celiac arteriography. There are numerous linear shadows within the portal vein during the arterial phase.

larger tumors, because of central necrosis, tumor stain is more apparent at the periphery, the central portion showing filling defect or uneven density.

Arterial stretching, displacement and distortion. In 46 cases these signs are commonly seen in primary hepatic carcinoma, the larger the tumor, the more conspicuous they are. We demonstrate displacement and stretching signs clearly in an arteriogram of a hepatic carcinoma in a cadaver (Figs 6,7).

Vascular encasement (38 cases). Normally, the hepatic arteries branch proportionately and taper peripherally with smooth lumens. In hepatic carcinoma, the arteries are invaded and then encircled by tumor with vascular encasement formed. The typical signs are vascular lumen irregular serration and vessel rigidity (Fig 8).

Intrahepatic filling defects or irregular mottling (13 cases). With injection of large amounts of contrast medium in celiac arteriograms, the hepatic parenchyma often shows delayed opacification, with simultaneous filling of the main trunks of the splenic and portal veins. Normal hepatic parenchyma appears homogeneous in density while necrotic cancerous areas show filling defects or irregular nonhomogeneous density (Figs 9,10).

Arterio-venous shunt (24 cases). With the presence of abnormal shunts between the hepatic artery and portal vein, the portal vein and its branches opacify during the arterial phase of hepatic arteriography. According to Okuda et al³ this sign is commonly seen in nearly 63.2%. This early opacification of portal branches occurs frequently at the liver periphery, hepatic arteries and portal veins being shown simultaneously, giving rise to the "double-tract" sign (Fig 11).

Pool or lake-like collections of contrast medium (44 cases). Many appear during the arterial phase and disappear slowly, remain-

ing visible after the arteries emptied. The pathologic basis of this sign is probably irregular dilation of venous sinusoids.

Tumor emboli formation within the portal vein (17 cases). This condition is not rare. Okuda et al⁴ pointed out that when the portal vein and its main branches are involved by tumor emboli, linear streaks of radiolucency or "thread and streak" sign is seen in the involved veins within 3-5 seconds after contrast medium injection. This sign is observed in 6 of our series (Fig 12).

In primary hepatic carcinoma, these arteriographic signs do not appear singly, usually several signs appear simultaneously. As most hepatic carcinoma develops on the basis of liver cirrhosis, hepatic artery hair-like coiling, liver shrinkage, splenomegaly and splenic artery dilation are often seen.

DISCUSSION

Technical considerations. It is essential that the catheter tip be properly placed. According to the literature,⁵ the celiac artery orifice is situated at T₁₂ level and that of the superior mesenteric artery is situated just a little bit below, both being ventrally placed. Our material also shows that most celiac arteries are situated at T₁₂ level or adjacent to its intervertebral space lower border. By placing a lead mark on the patient's abdominal skin before catheterization as a guide, much time is saved. Keeping the tip of the catheter ventralwards and sliding it up and down around this level, the desired artery is easily entered. We succeeded in 94 of 98 catheterizations, a 96% success.

It is also important to inject a few ml of contrast medium to assure exact placement of the catheter tip to avoid complications. Care should be taken to prevent entry of the catheter into the intercostal or lumbar artery. These arteries are of smaller calibre and are somewhat horizontally positioned. When these arteries are entered, injection of a few

ml of contrast medium evoke loin pain and the catheter should be immediately withdrawn into the abdominal aorta.

Films should be taken at the arterial, capillary and venous phase, the arterial phase is of major importance in demonstrating tumor vessels. Serial films are taken at 1/sec for the first 5 seconds, followed by proper intervals, X-rays being taken for 20 seconds.

Optimum injection pressure is important to prevent catheter tip recoil which displaces it from the proper position. The rate of injection is generally 12-15 ml/sec in celiac SA. We have obtained good results with a Gidlund injector at 3-4 kg/cm² injection pressure. Kaudot et al⁶ have studied the results of fast injection versus slow injection in hepatic arteriography, slow injection being 2.5-5 ml/sec with a total volume of 50 ml contrast medium being injected in 10-12 seconds. They achieved better results with the slow method.

Some authors^{7,8} prefer pharmaceutical enhancement in arteriography. Two kinds of drugs are used, one is a vasoconstrictor, such as adrenaline or angiotensin. According to Ekelund, they cause all normal vessels to contract, but not tumor vessels, thus allowing the latter to be more satisfactorily filled and opacified. The other is a vasodilator such as prisolone, which will reduce the resistance and increase the blood flow by dilating the arterioles thus enhancing opacification in the capillary and venous phases.

Normal anatomy and variations of the hepatic artery. The liver blood supply usually comes from the celiac trunk of the common hepatic artery. The common hepatic artery gives off right, middle and left branches, the former is the largest. Reuter reported that all the liver blood supply can be shown by common hepatic arteriography in 55-56% of the cases. In 25%, the left

hepatic artery arises from the left gastric artery. In 14% the right hepatic artery originates from the superior mesenteric artery. Rarely the right hepatic artery arises from the celiac artery, aorta or left gastric artery and the left hepatic artery from the aorta or superior mesenteric artery.

In our series, in 3 cases the hepatic artery arises from the superior mesenteric artery and in 9 the left hepatic artery arises from the superior mesenteric artery and in 9 the left hepatic artery originates from the left gastric artery. It is therefore very important to be familiar with the normal anatomy and variations of hepatic vasculature before performing hepatic angiography. All the hepatic vessels must be demonstrated so that the tumor is not missed. In hepatic angiography, celiac SA should be done first, in order to avoid non-filling of the branches of hepatic artery due to variations, especially of the left branch. Superselective hepatic arteriography and superior mesenteric SA may be performed subsequently, if necessary.

After ligation of the hepatic artery, the condition of a growing hepatic tumor may be shown by its collateral circulation blood supply. In 1 of our cases in which ligation of the hepatic artery was done 1 year previously, a large right liver lobe carcinoma was clearly shown by superior mesenteric SA.

SA evaluation. Our previous studies with transumbilical vein hepatography show that it is a simple method and has value in localizing hepatic carcinoma, but as the blood supply of hepatic carcinomas comes from the hepatic artery, umbilical venography cannot demonstrate the tumor vessels directly so its value is limited in small hepatic carcinoma diagnosis.⁹

SA shows the tumor vessels directly, locating even small carcinomas. In our series, the carcinomas were within 5 cm diameter in 9 cases, the smallest 1 being only 1.5 cm

diameter. 8 were symptomless and were discovered through general survey and confirmed by SA.

In comparing the results of arteriography with that of isotopic scans in 88 cases of hepatic carcinoma, 25 cases negative by isotope scan had the diagnosis established by arteriography. This indicates that the latter is superior and is a valuable new measure for diagnosing primary hepatic carcinoma.

SA not only gives definite diagnosis, but also shows the extent of the disease. According to Okuda et al¹⁰ correlation between the arteriographic and gross pathologic findings shows that hepatic carcinomas may be classified by their arteriographic findings and indications for surgery may be evaluated.

In our series the SA was not only used for diagnosis, it was also used for therapy such as injection of anticancer drugs and other medication when necessary.

No serious complications were encountered in our series. Goldstein¹¹ performed liver function tests both before and after SA and superselective arteriography in 26 cases, temporary GPT rise was found in only 2. Baum indicated that no ill effects are produced following angiography even if the prothrombin time is 20-25% below normal. Therefore we believe that SA is comparatively a safe and effective method for primary hepatic carcinoma diagnosis.

REFERENCES

1. Boijesen E, et al: Roentgenologic

diagnosis of primary carcinoma of the liver. *Acta Radiol* 3:257, 1965.

2. Renter SR, et al: *Gastrointestinal Angiography*. p 38, Saunders, Philadelphia, 1972.

3. Okuda K, et al: Angiographic demonstration of intrahepatic arteriportal anastomosis in hepatocellular carcinoma. *Radiology* 122:53, 1977.

4. Okuda K, et al: Demonstration of growing casts of hepatocellular carcinoma in the portal vein by celiac angiography: The thread and streaks sign. *Radiology* 117:303, 1975.

5. Margulin AR, et al: *Alimentary Tract Roentgenology*. ed 2, p 1391, Mosby, St, Louis, 1973.

6. Kauda J, et al: Slow injection hepatic angiography: A comparison with a high injection rate. *Acta Radiol* 14:700, 1973.

7. Ekelund L, et al: Pharmacangiography with Angiotensin. *Radiology* 110:533, 1974.

8. Goldstein HM, et al: Priscoline augmented hepatic angiography. *Radiology* 119:275, 1976.

9. Department of Radiology, Zhongshan Hospital, Shanghai First Medical College: Transumbilical vein hepatography in primary hepatic carcinoma: Roentgen appearance. *Chin Med J* 2:117, 1976.

10. Okuda K, et al: Angiographic assessment of gross anatomy of hepatocellular carcinoma: Comparison of celiac angiograms and liver pathology in 100 cases. *Radiology* 123:21, 1977.

11. Goldstein HM: Biochemical evaluation of liver and pancreas following selective and subselective angiography. *Radiology* 111:293, 1974.

